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(54) Title: PROPANOIC ACID DERIVATIVES AS INTEGRIN INHIBITORS

(54) Titre: DERIVES D'ACIDE PROPANOIQUE UTILISES EN TANT QU'INHIBITEURS DES INTEGRINES

(57) Abstract

Propanoic acid derivatives of formula (1) are described: Ar-X1¿-Ar1¿-Z-R in which Ar is a nitrogen base containing group; X1¿ is linker atom or group; Ar1¿ is an optionally substituted 5- or 6-membered nitrogen-containing aromatic or non-aromatic monocycle; Z is a group -CH(R13¿)CH¿2- [in which R13¿ is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], -C(R12a¿)(R13¿)-CH(R12b¿)- [in which R12a¿ and R12b¿ together with the carbon atoms to which they are attached form a C¿3-7cycloalkyl group] or C(R13¿)=CH-; R is a carboxylic acid (-CO¿2H) or a derivative or biostere thereof; and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of 'alpha'¿V integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

(57) Abrégé

L'invention se rapporte à des dérivés d'acide propanoïque représentés par la formule (1), Ar-X1¿-Ar1¿-Z-R, dans laquelle Ar est un groupe contenant une base azotée, X1¿ est un groupe ou un atome de liaison, Ar1¿ est un monocycle, non aromatique ou aromatique, comportant 5 ou 6 éléments et contenant de l'azote; Z est un groupeCH(R13¿)CH¿2- [dans lequel R13¿ est un groupe aliphatique, cycloaliphatique, hétéroaliphatique, hétérocycloaliphatique, aromatique ou hétéroaromatique éventuellement substitué],C(R12a¿)(R13¿)-CH(R12b¿)- [où R12a¿ et R12b¿ forment ensemble, en association aux atomes de carbone auxquels ils ont fixés, un groupe cycloakyle C¿3-7] ou C(R13¿)=CH-; R est acide carboxylique (-CO¿2H) ou un dérivé ou biostère de cet acide. L'invention se rapporte également aux sels, produits de solvatation, hydrates et N-oxydes des dérivés de l'acide propanoïque. Les composés permettent d'inhiber la liaison des intégrines 'alpha'¿V à leurs ligands et s'avèrent utiles pour la prophylaxie et le traitement des troubles immunitaires et inflammatoires.

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Propanoic acid derivatives of formula (1) are described: Ar–X^1–Ar^1–Z–R in which Ar is a nitrogen base containing group; X^1 is linker atom or group; Ar^1 is an optionally substituted 5– or 6–membered nitrogen–containing aromatic or non–aromatic monocycle; Z is a group –$CH(R^{13})CH_2$– [in which R^{13} is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], –$C(R^{12a})(R^{13})$–$CH(R^{12b})$– [in which R^{12a} and R^{12b} together with the carbon atoms to which they are attached form a C_{3-7}cycloalkyl group] or $C(R^{13})$=CH–; R is a carboxylic acid (–CO_2H) or a derivative or biostere thereof; and the salts, solvates, hydrates and N–oxides thereof. The compounds are able to inhibit the binding of αv integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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Description

PROPANOIC ACID DERIVATIVES AS INTEGRIN INHIBITORS

This invention relates to a series of propanoic acid derivatives, to compositions containing them, to processes for their preparation and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of a cell with other cells or components of the extracellular matrix plays an important role in regulating its response to external stimuli such as chemotactic factors, growth factors, cytokines, and inflammatory mediators [Juliano and Haskill, J. Cell Biol. 120 577-585 (1993); Miyamoto *et al* J. Cell Biol. 135, 1633-1642 (1996)]. Furthermore, the physical attachment of cells to other cells or surfaces may be crucial for development of some normal physiological responses.

In many disease states normal physiological responses are inappropriately triggered and are detrimental to the well being of the host. Since adhesion molecules play a role in the physical interactions of cells, antagonists of adhesion molecules may be able to inhibit some of the detrimental biological responses found in many disease states.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in informing a cell about the nature of its extracellular environment is the integrin family. Members of this family are involved in helping to regulate processes such as proliferation, apoptosis, migration and gene expression in a range of different cell types. They have also been shown to play a key role in regulating immune and inflammatory responses.

The integrin family of cell surface adhesion molecules has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg A. Current Topics in Microbiology and Immunology, 184 (1993)]. The members of the family are typically named according to their

heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin $\alpha_v\beta_3$ consists of the alpha v chain non-covalently linked to the beta 3 chain.

Some integrin chains are capable of pairing with more than one partner. For example, the alpha v chain has also been reported to pair with the beta 1 chain, the beta 5 chain, the beta 6 chain and the beta 8 chain to give molecules which bind to different sets of ligands and which are referred to respectively as the integrins $\alpha_v\beta_1$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ and $\alpha_v\beta_8$.

Integrins containing the α_v subunit form a family of integrins which generally (but not always) bind to vitronectin although several of them will bind to a range of other matrix molecules and/or cell surface molecules. For example $\alpha_v\beta_3$ will bind to molecules such as vitronectin, fibronectin, fibrinogen, osteopontin, bone sialoprotein, thrombospondin, pro von Willebrand factor and CD31.

The importance of integrin function in normal physiological responses is highlighted by two human deficiency diseases in which integrin function is defective. Thus, in the disease termed Leukocyte Adhesion Deficiency (LAD) there is a defect in one of the families of integrins expressed on leukocytes. Patients suffering from this diesease show a dramatically reduced ability to recruit leukocytes to inflammatory sites. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integrin family) there is a defect in blood clotting.

The interaction of cells with components of the extracellular environment via receptors containing α_v has been reported to be involved in a number of cellular responses which may be important in human disease states. These include endothelial cell proliferation and angiogenesis [Friedlander M, *et al*, Science 270, 1500-1502 (1995)], coronary smooth muscle cell migration, proliferation and extracellular matrix invasion [Panda, D., PNAS, 94, 9308-9313 (1997)], regulation of other integrin molecules on different cell types [Blystone, S D. J. Cell Biol. 127, 1129-1137 (1994); Imhof, B. Eur. J. Immunol, 27, 3242-3252 (1997)] and bone resorption [Ross F.P. *et*

al, J. Biol. Chem. 268 9901-9907 (1993)]. Furthermore, the α_V receptor has been reported to bind to the protease MMP-2 and this may also modify cell function [Brooks P.C. *et al*, Cell, 92, 391-400 (1998)].

Monoclonal antibodies and peptides have also been used to demonstrate in animal models that potentially beneficial changes in physiology can be achieved by blocking the function of α_V-containing integrin receptors. For example, Mitjans F. *et al* [Journal of Cell Science, 108, 2825-2838 (1995)] showed that in a mouse model an antibody that bound to the α_V chain inhibited tumour development and metastasis. Brooks P.C., *et al;* [J. Clin. Invest. 96, 1815-1822 (1995)] demonstrated that an antibody that blocked the function of $\alpha_V\beta_3$ inhibited the growth of a tumour implanted into a piece of human skin grafted on to a SCID mouse. Christofidou-Solomidou M, [Am. J. Pathol. 151, 975-983 (1997)] has reported that an anti-α_V monoclonal antibody inhibited angiogenesis at the site of wound healing. Hammes H-P, *et al*, [Nature Medicine, 2, 529-533 (1996)] showed that an α_V integrin antagonist cyclic peptide inhibited retinal neovascularisation in a model which may have relevance to the human disease states of retinopathy and senile macular degeneration. Srivata S, *et al* [Cardiovascular Research 36, 408-428 (1997)] have reported that in an animal model a peptidic $\alpha_V\beta_3$ antagonist can limit neointimal hyperplasia and luminal stenosis.

$\alpha_V\beta_3$ has been reported to bind to a molecule expressed on endothelial cells termed CD31 [Piali L. *et al*, J. Cell Biol. 130, 451-460 (1995)]. Thus $\alpha_V\beta_3$ may play a role in leukocyte extravasation. It has also been shown to be capable of co-stimulating T-cell degranulation [Ybarrondo B. Immunology, 91, 186-192 (1997)]. Inhibition of α_V function may down regulate immune and/or inflammatory responses.

$\alpha_V\beta_3$ has also been shown to play a role in the ingestion of apoptotic cells by macrophages [Akbar A.N. *et al*, J. Exp. Med 180, 1943-1947 (1994)]. The rapid phagocytosis of apoptotic cells may be a physiological method of reducing inflammatory responses associated with cell lysis. The modulation of $\alpha_V\beta_3$ function may alter the inflammatory responses

mounted in regions of apoptosis. In some disease states this may be beneficial.

It has also been shown that members of the α_v family play a key role in the ability of osteoclasts to resorb bone. An imbalance between bone formation and resorption can lead to major health problems. Blockade of α_v containing receptors can inhibit bone resorption in an animal model [Engleman V.W. *et al* J. Clin. Invest. 99, 2284-2292, (1997)] and this suggests that α_v antagonists may be useful in the treatment of human diseases such as osteoporosis, Paget's disease, humoral hypercalcaemia of malignancy and metastic bone disease.

α_v containing receptors are often upregulated at sites of angiogenesis where this occurs for example in tumours, and some pathological conditions. Arap W, *et al* [Science, 279, 377-380, (1998)] have shown that peptides that bind to α_v containing receptors can be used to deliver drugs to such sites and an antibody recognising an α_v integrin has been shown to be capable of imaging tumour vasculature [Sipkins D.A. *et al* Nature Medicine, 4, 623-626 (1998].

The tissue distribution and range of ligands of different members of the α_v integrin family suggests that these molecules may have different physiological roles. This view is supported by Friedlander M *et al* [Science, 270, 1500-1502, (1995)] who showed that angiogenesis associated with different growth factors was dependent on different α_v containing integrins.

Inhibition of an α_v-mediated cell interaction can be expected to be beneficial in a number of disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is important to be able to identify selective inhibitors of the α_v subgroup.

We have now found a group of compounds which are potent and selective inhibitors of α_v integrins. Members of the group are able to inhibit α_v

integrins such as $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ at concentrations at which they generally have no or minimal inhibitory action on integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of diseases or disorders involving inappropriate growth or migration of cells as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1):

$$Ar—X^1—Ar^1—Z—R \qquad (1)$$

wherein:

(1) Ar is a group $R^{1a}N(R^2)L^1Ar^2$- in which:

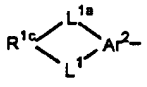
$R^{1a}N(R^2)$ is a nitrogen base;

L^1 is a -$C(R^3)(R^4)$- [where R^3 and R^4, which may be the same or different, is each a hydrogen atom, a straight or branched alkyl group or a hydroxyl group], -C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -P(O)-, -P(O)(OR^a)- [where R^a is a hydrogen atom or a straight or branched C_{1-6}alkyl group] or -P(O)(OR^a)O- group; and

Ar^2 is an optionally substituted six-membered 1,4-arylene or 1,4-heteroarylene ring; or

(2) Ar is a group $R^{1b}Ar^2$ in which R^{1b} is a cyclic or acyclic nitrogen base and Ar^2 is as just defined; or

(3) Ar is a bicyclic ring:



in which R^{1c} is a nitrogen base, L^1 and Ar^2 are as just defined and -L^{1a}- is a covalent bond a -$(CH_2)_2$- or -$(CH_2)_3$- group or a group L^1 as just defined; or

(4) Ar is a group $R^{1d}L^1Ar^2$- in which R^{1d} is a nitrogen base and L^1 and Ar^2 as just defined;

X^1 is an -O- or -S- atom or a group selected from -C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -$C(R^5)(R^6)$- {where R^5 is a hydrogen atom or an optionally substituted straight or branched alkyl group and R^6 is a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy,

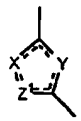
alkylthio, aromatic, heteroaromatic, or -$(Alk^1)_mR^7$ group [in which Alk^1 is a C_{1-3}alkylene chain, m is zero or the integer 1 and R^7 is a -OH, -SH, $-NO_2$, -CN, $-CO_2H$, $-CO_2R^8$ (where R^8 is an optionally substituted straight or branched C_{1-6}alkyl group), $-SO_3H$, $-SOR^8$, $-SO_2R^8$, $-OCO_2R^8$, C(O)H, $-C(O)R^8$, $-OC(O)R^8$, $-C(S)R^8$, $-NR^9R^{10}$ (where R^9 and R^{10}, which may be the same or different is each a hydrogen atom or a straight or branched alkyl group), $-C(O)N(R^9)(R^{10})$, $-OC(O)N(R^9)(R^{10})$, $-N(R^9)C(O)R^{10}$, $-CSN(R^9)(R^{10})$, $-N(R^9)C(S)R^{10}$, $-SO_2N(R^9)(R^{10})$, $-N(R^9)SO_2R^{10}$, $-N(R^9)C(O)N(R^{10})(R^{11})$ [where R^{11} is a hydrogen atom or a straight or branched alkyl group], $-N(R^9)C(S)N(R^{10})(R^{11})$, $-N(R^9)SO_2N(R^{10})(R^{11})$, aromatic or hetero-aromatic group] or $-N(R^5)-$;

Z is a group $-CH(R^{13})CH_2-$ [in which R^{13} is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], $-C(R^{12a})(R^{13})-CH(R^{12b})-$ [in which R^{12a} and R^{12b} together with the carbon atoms to which they are attached form a C_{3-7}cycloalkyl group] or $-C(R^{13})=CH-$;

R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;

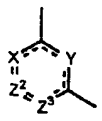
Ar^1 is an optionally substituted 5- or 6-membered nitrogen-containing aromatic or non-aromatic monocycle selected from:

(A)



where one of X and Y is a nitrogen atom and the other is a nitrogen, oxygen or sulphur atom, Z^1 is a carbon, nitrogen, oxygen or sulphur atom and the broken line (- -) represents saturation or unsaturation; or

(B)



where X, Y and the broken line are as just defined and Z^2 and Z^3 is each a carbon, nitrogen, oxygen or sulphur atom;
and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (E or Z isomers). The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

In the compounds of the invention as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to substituents are to be understood to include the following atoms or groups unless specified otherwise.

Thus as used herein the term "optionally substituted straight or branched alkyl", whether present as a group or part of a group includes optionally substituted straight or branched C_{1-6}alkyl groups, for example C_{1-4}alkyl groups such as methyl, ethyl, n-propyl, i-propyl or t-butyl groups. Similarly, the terms "optionally substituted straight or branched alkenyl" or "optionally substituted straight or branched alkynyl" are intended to mean C_{2-6}alkenyl or C_{2-6}alkynyl groups such as C_{2-4}alkenyl or C_{2-4}alkynyl groups. Optional substitutents present on these groups include those optional substituents mentioned hereinafter in relation to R^2 optionally substituted aliphatic groups.

The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

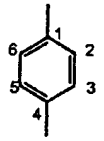
The term "straight or branched haloalkyl" is intended to include the alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-CF_3$, $-CCl_3$, $-CHF_2$- $-CHCl_2$, $-CH_2F$, and $-CH_2Cl$ groups.

The term "straight or branched alkoxy" as used herein is intended to include straight or branched C_{1-6}alkoxy e.g. C_{1-4}alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy. "Haloalkoxy" as used herein includes any of those alkoxy groups substituent by one, two or three halogen atoms as described above. Particular examples include $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$ and $-OCH_2Cl$ groups.

As used herein the term "straight or branched alkylthio" is intended to include straight or branched C_{1-6}alkylthio, e.g. C_{1-4}alkylthio such as methylthio or ethylthio groups.

The terms "aromatic" or heteroaromatic" are intended to include those optionally substituted aromatic or heteroaromatic groups described generally and particularly hereinafter in relation to the groups R^2, R^{14}, R^{15} and R^{16}.

Where the term "1,4-arylene" is used in relation to Ar^2 in the formulae herein this is to be understood to mean a ring :



in which the carbon atoms at the one and four positions are attached to the remainder of the molecule. The term "1,4-heteroarylene" is to be understood to mean an equivalent ring structure in which one or more of the carbon atoms at the 2-, 3-, 5- and/or 6-positions of the 1,4-arylene ring is replaced by a nitrogen atom.

Such arylene and heteroarylene rings may be optionally substituted, each substituent being attached to a carbon atom, where present, at the 2-, 3-, 5- and/or 6-positions. Particular substituents include halogen atoms, or straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy or alkylthio groups, or -OH, $-CO_2H$, $-CO_2R^8$, -CN, $-NH_2$, $-NO_2$ or straight or branched alkylamino or dialkylamino groups.

Nitrogen bases represented by the group $R^{1a}N(R^2)$- in compounds of the invention include acyclic or cyclic nitrogen bases containing two, three or more nitrogen atoms. Such bases will generally include one or more carbon atoms and optionally one or more other heteroatoms such as oxygen or suphur atoms.

Particular examples of acyclic nitrogen bases represented by the group $R^{1a}N(R^2)$- include those wherein R^{1a} is a $R^{14}R^{15}NC(X^2)$- or $R^{15}C(=NR^{14})$- group, in which X^2 is a $=NR^{16}$, =O, =NCN, $=NC(O)NH_2$ or =S group, and each of R^2, R^{14}, R^{15} and R^{16}, which may be the same or different, is a hydrogen atom or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group.

Optionally substituted aliphatic groups represented by R^2, R^{14}, R^{15} and/or R^{16} in the bases $R^{1a}N(R^2)$- include optionally substituted C_{1-10} aliphatic groups. Particular examples include optionally substituted straight or branched C_{1-10}alkyl, e.g. C_{1-6}alkyl, C_{2-10}alkenyl, e.g. C_{2-6}alkenyl or C_{2-10}alkynyl e.g. C_{2-6}alkynyl groups.

Heteroaliphatic groups represented by R^2, R^{14}, R^{15} and/or R^{16} include the aliphatic groups just described but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples of suitable L^2 atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2$-, $-N(R^{17})$- [where R^{17} is a hydrogen atom or an optionally substituted straight or branched alkyl group], $-CON(R^{17})$-, $-OC(O)N(R^{17})$-, $-CSN(R^{17})$-, $-N(R^{17})CO$-, $-N(R^{17})C(O)O$-, $-N(R^{17})CS$-, $-S(O)_2N(R^{17})$-, $-N(R^{17})S(O)_2$-, $-N(R^{17})CON(R^{17})$-, $-N(R^{17})CSN(R^{17})$-, or $-N(R^{17})SO_2N(R^{17})$- groups. Where the linker group contains two R^{17} substituents, these may be the same or different.

Particular examples of aliphatic groups represented by R^2, R^{14}, R^{15} and/or R^{16} include optionally substituted $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_2$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, $-CHCH_2$, $-CHCHCH_3$, $-CH_2CHCH_2$, $-CHCHCH_2CH_3$, $-CH_2CHCHCH_3$, $-(CH_2)_2CHCH_2$, $-CCH$, $-CCCH_3$, $-CH_2CCH$, $-CCCH_2CH_3$, $-CH_2CCCH_3$, or $-(CH_2)_2CCH$ groups. Where appropriate each of said groups may be optionally interrupted by one or two atoms and/or groups L^2 to form an optionally substituted hetero-aliphatic group. Particular examples include optionally substituted $-L^2CH_3$, $-CH_2L^2CH_3$, $-L^2CH_2CH_3$, $-CH_2L^2CH_2CH_3$, $-(CH_2)_2L^2CH_3$, $-L^2(CH_2)_2CH_3$ and $-(CH_2)_2L^2CH_2CH_3$ groups.

The optional substituents which may be present on aliphatic or heteroaliphatic groups represented by R^2, R^{14}, R^{15}, and/or R^{16} include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, or C_{1-6}alkoxy, hydroxy, thiol, C_{1-6}alkylthio, optionally substituted C_{6-12}arylamino, substituted amino groups or optionally substituted aromatic or heteroaromatic groups. Substituted amino groups include $-NHR^{18}$ and $-N(R^{18})_2$ groups where R^{18} is a straight or branched alkyl group. Where two R^{18} groups are present these may be the same or different. Particular examples of substituted groups represented by R^2, R^{14}, R^{15} and/or R^{16} include those specific groups just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example groups of the type $-CH_2CF_3$, $-CH(CF_3)_2$, $-CH_2CH_2CF_3$, $-CH_2CH(CF_3)_2$ and $-C(CF_3)_2CH_3$, or substituted by one or two optionally substituted aromatic or heteroaromatic groups, for example optionally substituted phenyl, pyridinyl or pyrimidinyl groups.

Optionally substituted cycloaliphatic groups represented by R^2, R^{14}, R^{15} and/or R^{16} include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g C_{3-7} cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by R^2, R^{14}, R^{15} and/or R^{16} include optionally substituted C_{3-10}heterocycloaliphatic

groups. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7}heterocycloalkyl, or C_{3-10}heterocycloalkenyl, e.g. C_{3-7} hetercycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^2 as just defined.

Optionally substituted polycycloaliphatic groups represented by R^2, R^{14}, R^{15} and/or R^{16} include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by R^2, R^{14}, R^{15} and/or R^{16} include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^2 atoms or groups.

Particular examples of R^2, R^{14}, R^{15} and/or R^{16} cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloalliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbomyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the R^2, R^{14}, R^{15} and R^{16} cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups include one, two, three or more of those substituents described above in relation to R^2 aliphatic or heteroaliphatic groups. Additionally R^2, R^{14}, R^{15} and R^{16} cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups may be optionally substituted by straight or branched alkyl, alkenyl, alkynyl or haloalkyl groups.

Optionally substituted aromatic groups represented by the groups R^2, R^{14}, R^{15} and/or R^{16} in a base represented by $R^{1a}N(R^2)$- include for example monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups. Each of these aromatic groups may be optionally substituted by one, two, three or more R^{19} atoms or groups as defined below.

Heteroaromatic groups represented by the groups R^2, R^{14}, R^{15} and/or R^{16} include for example C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, benzotriazolyl, indolyl, indolinyl, isoindolyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, qunoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the groups R^2, R^{14}, R^{15} and/or R^{16} include one, two, three or more substituents, each selected from an atom or group R^{19} in which R^{19} is $-R^{19a}$ or $-Alk^3(R^{19a})_m$, where R^{19a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{20}$ [where R^{20} is an $-Alk^3(R^{19a})_m$, aryl or heteroaryl group], $-CSR^{20}$, $-SO_3H$, $-SO_3R^{20}$, $-SOR^{20}$, $-SO_2R^{20}$, $-SO_2NH_2$, $-SO_2NHR^{20}$, $-SO_2N(R^{20})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{20}$, $-CSNHR^{20}$, $-CON[R^{20}]_2$, $-CSN(R^{20})_2$, $-N(R^{21})SO_2R^{20}$, [where R^{21} is a hydrogen atom or a straight or branched alkyl group] $-N(SO_2R^{20})_2$, $-N(R^{21})SO_2NH_2$, $-N(R^{21})SO_2NHR^{20}$, $-N(R^{21})SO_2N(R^{20})_2$, $-N(R^{21})COR^{20}$, $-N(R^{21})CONH_2$, $-N(R^{21})CONHR^{20}$, $-N(R^{21})CON(R^{20})_2$, $-N(R^{21})CSNH_2$, $-N(R^{21})CSNHR^{20}$, $-N(R^{21})CSN(R^{20})_2$, $-N(R^{21})CSR^{20}$, $-N(R^{21})C(O)OR^{20}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^{21})$-, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{21})SO_2NHet^1$, $-N(R^{21})CONHet^1$, $-N(R^{21})CSNHet^1$, $-SO_2N(R^{21})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{21})$-, -C(O)- or -C(S)- groups], $-Het^2$, $-CON(R^{21})Het^2$, $-CSN(R^{21})Het^2$, $-N(R^{21})CON(R^{21})Het^2$, $-N(R^{21})CSN(R^{21})Het^2$, aryl or heteroaryl group; Alk^3 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{21})$- groups; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{20} or R^{21} groups are present in one of the above substituents, the R^{20} or R^{21} groups may be the same or different.

When in the group $-Alk^3(R^{19a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{19a} may be present on any suitable carbon atom in $-Alk^3$. Where more than one R^{19a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^3$. Clearly, when m is zero and no substituent R^{19a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^3 becomes an alkyl, alkenyl or alkynyl group.

When R^{19a} is a substituted amino group it may be for example a group $-NHR^{20}$ [where R^{20} is as defined above] or a group $-N(R^{20})_2$ wherein each R^{20} group is the same or different.

When R^{19a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{19a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{20}$ or a $-SR^{20}$ or $-SC(=NH)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^{19a} include groups of formula $-CO_2Alk^4$ wherein Alk^4 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^4 group include R^{19a} substituents described above.

When Alk^3 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{21})-$ groups.

Aryl or heteroaryl groups represented by the groups R^{19a} or R^{20} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group R^2. The aromatic

and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -NHet^1 or -Het^2 forms part of a substituent R^{19} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, imidazolidinyl, oxazolidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet^1 or -Het^2 include those substituents described above in relation to R^6.

Particularly useful atoms or groups represented by R^{19} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted C_{3-10}cycloalkyl e.g. cyclopentyl or cyclohexyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, thiazolidinyl or piperidinyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy, ethoxy, or isopropyloxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, optionally substituted C_{6-12}arylC_{1-6}alkylamino e.g. benzylamino, amino (-NH_2), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, aminoC_{1-6}alkylamino e.g. amino-methylamino, Het^{1}NC_{1-6}alkylamino, e.g. morpholinopropylamino, C_{1-6}alkyl-aminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC_{1-6}alkylamino e.g. hydroxyethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro,

cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^4$ [where Alk^4 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(=NH)NH_2$, sulphonyl ($-SO_3H$), $-SO_3Alk^4$, C_{1-6}alkylsulphinyl e.g. ethylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, $-CONHC(=NH)NH_2$, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxy-

carbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g.benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{19} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{19} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^2, R^{14}, R^{15} and/or R^{16}.

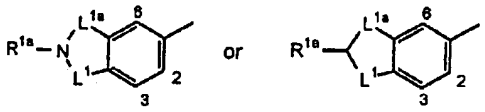
Particular examples of cyclic nitrogen bases represented by the group $R^{1a}N(R^2)$- in compounds of the invention include those wherein R^{1a} is an optionally substituted four- to ten-membered, for example six-membered, mono- or bicyclic fused-ring cycloaliphatic or aromatic group containing one, two, three or more nitrogen atoms and optionally one or more other heteroatoms such as oxygen and sulphur atoms. Suitable examples include optionally substituted pyrrolidinyl, pyrrolinyl, piperidinyl, tetrahydropyridinyl, piperazinyl, tetrahydropyrimidinyl, homopiperazinyl, triazinyl, morpholinyl, thiomorpholinyl, thiazolinyl, thiazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinlinyl, pyrrolyl, pyrazolyl, imidazolyl, imidazolinyl, imidazolidinyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, oxazolidinyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, triazinyl, quinolinyl and isoquinolinyl groups. Optional substituents which may be present on these groups include one, two or three of those R^{19} substituents described herein. The ring R^{1a} will generally be attached to the -N(R^2)- group through any available ring carbon atom.

Cyclic nitrogen bases represented by the group R^{1b} in compounds of the invention include those optionally substituted four- to ten- membered mono- or bicyclic fused-ring cycloaliphatic or aromatic groups containing one, two, three or more nitrogen atoms and optionally one or more other heteroatoms as just generally and particularly described for the group R^{1a}.

The cyclic group R^{1b} may be attached to the adjacent Ar^2 group through a ring carbon atom, or where appropriate a ring nitrogen atom.

Acyclic nitrogen bases represented by the group R^{1b} in compounds of the invention include those acyclic groups as just generally and particularly described for the group R^{1a}.

When in the compounds of the invention the Ar group is a bicyclic ring it may be for example a ring of formula:



[where $R^{1a}N$ and $R^{1a}CH$ form the nitrogen base R^{1c} described in formula (1)] in which each of the carbon atoms at positions 2-, 3- and 6- may optionally be substituted or replaced by a nitrogen atom as described above in relation to the ring Ar^2. In these compounds R^{1a}, L^1 and L^{1a} may be as decribed previously. L^{1a} may in particular be a $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$ chain.

Nitrogen bases represented by the group R^{1d} in compounds of the invention include those acyclic and cyclic groups as just generally and particularly described for the group R^{1a}. The group R^{1d} may be attached to the adjacent L^1 group through a carbon atom, or where appropriate a nitrogen atom.

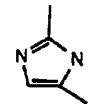
When in the compounds of the invention the group Z contains a group R^{13} which is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloalphatic, aromatic or heteroaromatic group, each of these groups may be any of those generally and previously particularly described for the group R^2. Optional substituents which may be present on such groups include those described for R^2, for example one, two or three R^{19} substituents as described above when R^{13} is an aromatic or heteroaromatic group. Additionally, when R^{13} is an aliphatic or

heteroaliphatic group it may be optionally substituted by an optionally substituted aromatic or heteroaromatic group of the type described above in relation to R^2.

When the group Z is $-C(R^{12a})(R^{13})-CH(R^{12b})-$, then R^{12a} and R^{12b} together with the carbon atoms to which they are attached may form for example a cyclopropyl group.

Derivatives of the carboxylic acid group R in compounds of the invention include caboxylic acid esters and amides. Particular esters and amides include $-CO_2Alk^4$ and $-CONR^9R^{10}$ groups as described herein. Biosteres of the carboxylic acid group R include tetrazoles, or other acids such as squaric acid, phosphoric acid, sulphonic acid, sulphinic acid, or boronic acid.

Aromatic or non-aromatic monocycles represented by Ar^1 in compounds of the invention include for example optionally substituted rings selected from: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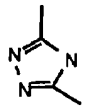
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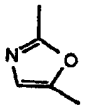
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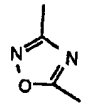
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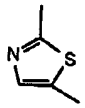
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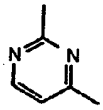
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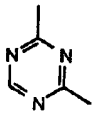
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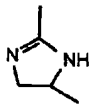
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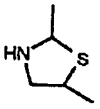
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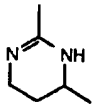


When a carbon atom is available in rings of these types , and in general in rings represented by Ar^1, it may be optionally substituted by a halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy or alkylthio group, or a -OH, $-CO_2H$, $-CO_2R^8$, -CN, $-NH_2$, $-NO_2$ or straight or branched alkylamino or dialkylamino group. Additionally, any suitable nitrogen atom when present may be optionally substituted, for example by a straight or branched alkyl group.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

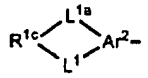
Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or

napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

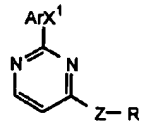
Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In one group of compounds of formula (1) Ar may be for example a group $R^{1a}N(R^2)L^1Ar^2$-, $R^{1b}Ar^2$ or a group:



in which R^{1a}, R^{1c}, R^2, L^1, L^{1a} and Ar^2 are as previously generally and particularly defined and R^{1b} is a cyclic nitrogen base.

A particularly useful group of compounds according to the invention has the formula (1a):



(1a)

in which Ar, X^1, Z and R are as defined for formula (1) and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formula (1a) and in general in compounds of the invention the pyrimidine ring may be additionally optionally substituted by one or two straight or branched alkyl, haloalkyl, haloalkoxy or alkoxy

groups, or -OH, $-CO_2H$, $-CO_2R^8$, -CN, $-NH_2$, $-NO_2$ halogen or straight or branched alkylamino or dialkylamino groups.

In compounds of formula (1a) and in general in compounds of the invention the group Z is preferably a $-CH(R^{13})CH_2-$ or $-C(R^{13})=CH-$ group. In these compounds the group R^{13} is preferably an optionally substituted aromatic or heteroaromatic group as defined herein. Particularly useful groups include optionally substituted phenyl and five- or six-membered heteroaromatic groups, e.g. optionally substituted pyridyl and pyrimidinyl groups.

In compounds of formula (1a) and in general in compounds of the invention the optional substituents on R^{13} groups include one or more substituents which may be the same or different selected from halogen atoms, especially fluorine, chlorine or bromine atoms, C_{1-6}alkyl groups, specially methyl, ethyl and i-propyl groups, carboxyl ($-CO_2H$) or esterified carboxyl ($-CO_2Alk^4$) groups, amino ($-NH_2$) or substituted amino groups, especially aminoC_{1-6}alkylaminocarbonyl groups e.g. aminoethylamino-carbonyl groups, hydroxyl or C_{1-6}alkoxy groups, especially methoxy, ethoxy and isopropyloxy, haloC_{1-6}alkyl groups, especially trifluoromethyl, haloC_{1-6}alkoxy groups, especially trifluoromethoxy, thiol (-SH) or thioC_{1-6}alkyl groups, especially thiomethyl, nitro, cyano, amidino, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl groups.

In the compounds of formula (1a) and in general in compounds of the invention, the group R is preferably a carboxylic acid ($-CO_2H$).

The group X^1 in general and in compounds of formula (1a) is preferably -O-, -S-, -NH- or $-N(R^5)-$. A particularly useful $-N(R^5)$ group is $-N(CH_3)-$.

Particularly useful compounds of the invention include those wherein Ar is a group $R^{1a}N(R^2)-L^1-Ar^2$. $R^{1b}Ar^2$ or $R^{1d}L^1Ar^2$ in which R^{1a}, R^{1b}, R^{1d}, R^2, L^1 and Ar^2 are as previously generally and particularly defined. In these compounds when Ar is a group $R^{1a}N(R^2)-L^1-Ar^2$, R^2 may be in particular a hydrogen atom. R^2 may be in particular a hydrogen atom. L^1 may in particular by a group $-C(R^3)(R^4)-$ or -C(O)- where R^3 and R^4 are as

previously generally and particularly defined. An especially useful L^1 group is $-CH_2-$. R^{1a} may in particular be a group $R^{14}R^{15}NC(X^2)-$, $R^{15}C(=NR^{14})-$ or an optionally substituted four- to ten-membered, particularly six-membered, nitrogen-containing aromatic group optionally containing one or more other heteroatoms as described herein in relation to R^{1a}. Particularly useful R^{1a} groups include $H_2NC(=NH)-$, imidazolinyl, benzimidazolyl and optionally substituted pyridyl groups. Especially useful optionally substituted pyridyl groups include pyridyl, 2-aminopyridyl and 2-methylaminopyridyl groups.

IIn these compounds when Ar is a group $R^{1b}Ar^2$, R^{1b} may in particular be a group $R^{14}R^{15}NC(X^2)$, $R^{15}C(=NR^{14})-$, or an optionally substituted four to ten membered, particularly five or six-membered, nitrogen containing heterocycloaliphatic or aromatic group optionally containing one or more other heteroatoms as described herein in relation to R^{1b}. Particularly useful R^{1b} groups include optionally substituted pyridyl and imidazoyl groups. Especially useful R^{1b} groups include a 2-aminopyridyl and 2-methylaminopyridyl group.

In these compounds when Ar is a group $R^{1d}L^1Ar^2$, R^{1d} may in particular be a group $R^{14}R^{15}NC(X^2)-$, $R^{15}C(=NR^{14})-$ or an optionally substituted four to ten membered, particularly five or six membered, nitrogen containing heterocycloaliphatic or aromatic group optionally containing one or more other heteroatoms as described herein in relation to R^{1a}. Particularly useful R^{1d} groups include $H_2NC(=NH)-$ and optionally substituted imidazoyl, imidazolinyl, triazolyl and pyridyl groups. In these compounds L^1 may be in particular a group $-C(R^3)(R^4)-$ where R^3 and R^4 are as previously generally and particularly defined. Particularly useful L^1 groups include $-CH_2-$ and $-CH(OH)-$.

In these compounds and in general in compounds of the invention Ar^2 is an optionally substituted six-membered 1,4-arylene, especially a 1,4-phenylene group.

Particularly useful compounds of the invention include:

3-(4-[2-Aminoethyl]benzamide)-3-(2-[4-[(2-pyridinylamino)methyl] phenoxy]-4-pyrimidinyl)propanoic acid;

3-(2-[4-[(4,5-Dihydro-1*H*-imidazol-2-ylamino)methyl]phenoxy)-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid;

3-[2-[4-([Amino(imino)methyl]amino)methyl)phenoxy]-4-pyrimidinyl]-3-(4-benzoic acid)propanoic acid;

3-[2-(4-[({Amino(imino)methyl}amino)methyl]-*N*-methylaniliino)-4-pyrimidinyl]-3-(4-fluorophenol)propanoic acid;

3-(3-Methoxyphenyl)-3-(2-[4-[(2-pyridinylamino)methyl]phenoxy]-4-pyrimidinyl)propanoic acid;

3-[2-(4-[6-Amino-2-pyridinyl}phenoxy)-4-pyrimidinyl]-3-(4-carboxy phenyl)propanoic acid;

3-[2-(4-[2-(*N*-methylamino)-6-pyridinyl}phenoxy)-4-pyrimidinyl]-3-(4-carboxyphenyl)propanoic acid;

3-(2-[4-[(1*H*-1,3-Benzimidazol-2-yl-amino)methyl}phenoxy]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid;

3-(3-Benzenecarboxylic acid)-3-(2-[4-[(2-pyridinylamino)methyl] phenoxy}-4-pyrimidinyl)propanoic acid;

and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent and selective inhibitors of α_V integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inappropriate growth or migration of cells. The invention extends to such a use and to the use of the compounds of formula (1) for the manufacture of a medicament for treating such diseases and disorders. Particular diseases include inflammatory diseases, and diseases involving angiogenesis, bone resorption or cellular or matrix over-expansion.

Particular uses to which the compounds of the invention may be put include the treatment or inhibition of tumour growth and metastasis;

retinopathy; macular degeneration psoriasis; rheumatoid arthritis; osteoporosis; bone resorption following or due to joint replacement, hypercalcemia of malignancy, Paget's disease, glucocorticoid treatment, immobilisation-induced osteopenia, hyperparathyroidism or peridontal disease; vascular restenosis; atherosclerosis; inflammatory bowel disease; and psoriasis.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal

administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. Many of the reactions describd are well-known standard synthetic methods which may be applied to a variety of compounds and as such can be used not only to generate compounds of the invention, but also where necessary the intermediates thereto.

In the following process description, the symbols R, Ar, X^1, Ar^1, L^1 and Z when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (1c):

$$Ar\text{-}X^1\text{-}Ar^1\text{-}Z\text{-}CO_2Alk^4 \qquad (1c)$$

where Alk^4 is an alkyl group, for example a C_{1-6}alkyl group as described above.

The hydrolysis may be performed using either an acid or base depending on the nature of Alk^4, for example an organic acid such as trifluoroacetic

acid optionally in an organic solvent such as a haloalkane e.g. dichloromethane, or an inorganic base such as sodium, lithium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at around ambient temperature to 60°C. Where desired mixtures of such solvents may be used.

Esters of formula (1c) in which X^1 is an -O- or -S- atom or -N(R^5)- group may be prepared by displacement of a leaving atom or group in a compound of formula (2):

$$RZAr^1L \qquad (2)$$

[where L is a leaving atom or group], with a reagent ArX^1H [where X^1 is as just defined].

The reaction may be performed at an elevated temperature, for example the reflux temperature, where necessary in the presence of a solvent, for example a substituted amide such as dimethylformamide, or an ether, e.g. a cyclic ether such as tetrahydrofuran, optionally in the presence of a base, for example a hydride such as sodium hydride or an organic amine such as pyridine, or an inorganic base such as cesium or potassium carbonate.

Particular examples of leaving groups represented by L in compounds of formula (2) include halogen atoms such as a chlorine or bromine atom, and sulphonyloxy groups, for example alkylsulphonyloxy groups such as a methylsulphonyloxy group.

Alternatively esters of formula (1c) in which X^1 is a -N(R^5)- group may be prepared by cross-coupling an amine of formula $ArN(R^5)H$ with an organic halide of formula Hal^5Ar^1ZR[where Hal^5 is a halogen atom such as a bromine or chlorine atom].

The reaction may be carried out in the presence of a metal complex catalyst such as a palladium complex e.g. dichloro[1,1'-bis(diphenyl-

phosphino)ferrocene]palladium(II), in the presence of an organic base, for example sodium-t-butoxide, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at an elevated temperature e.g. the reflux temperature.

Intermediate compounds of formula (2) in which Z is a $-CH(R^{13})CH_2-$ group and R is a $-CO_2Alk^4$ group may be prepared by reaction of an intermediate of formula (3):

$$R^{13}CH_2Ar^1L \quad (3)$$

with an α-haloester $HalCH_2CO_2Alk^4$ [where Hal is a halogen atom such as a bromine atom] in the presence of a strong base, e.g. a silazide such as sodium or lithium hexamethyldisilazide in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran at a low temperature, e.g. around -78°C.

Intermediates of formula (3) may be prepared by cross-coupling a halide of formula (4):

$$Hal^1CH_2Ar^1L \quad (4)$$

[where Hal^1 is a halogen atom such as a chlorine atom] with an organometallic reagent $R^{13}MHal^2$, where M is a metal atom such as a zinc atom, and Hal^2 is a halogen atom such as a bromine atom.

The reaction may be carried out in the presence of a metal catalyst, for example a metal complex catalyst such as a palladium complex, e.g. tetrakis(triphenylphosphine)palladium, in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at an elevated temperature e.g. the reflux temperature.

Intermediate compounds of formula (2) in which Z is a $-C(R^{13})=CH-$ group and R is a $-CO_2Alk^4$ group may be prepared by reaction of a ketone of formula (5):

$R^{13}COAr^1L$ (5)

with a phosphonate $(Alk^5O)_2P(O)CH_2CO_2Alk^4$ [where Alk^5 is a C_{1-6}alkyl group] in the presence of a base.

Suitable bases include organometallic bases, for example an organolithium compound such as n-butyllithium or lithium diisopropylamide, hydrides such as sodium or potassium hydride, alkoxides, such as sodium hydroxides, e.g. sodium methoxide, and cyclic amines, for example 1,8-diazabiacyclo[5.4.0]undec-7-ene.

The reaction may be performed in a suitable solvent, for example a polar aprotic solvent such as an amide, e.g. N,N-dimethylformamide; or a non-polar solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran or a halogenated hydrocarbon, e.g. dichloromethane. Preferably the reaction is carried out at a low temperature, for example from around -78°C to around ambient temperature.

Intermediate ketones of formula (5) may be obtained by reaction of a halide of formula (6):

Hal^3Ar^1L (6)

[where Hal^3 is a halogen atom such as a chlorine atom] by halogen-metal exchange with a base such as n-butyllithium, followed by reaction with a nitrile $R^{13}CN$, an acid chloride $R^{13}COCl$ or an ester $R^{13}CO_2Alk^5$ in a solvent such as tetrahydrofuran at a low temperature e.g. around -70°C and subsequent treatment with an acid such as hydrochloric acid at around ambient temperature.

In another process according to the invention a compound of formula (1) in which X^1 is a $-C(R^5)(R^6)-$ group may be prepared by cross-coupling a halogen of formula (7):

$RZAr^1Hal^4$ (7)

[where Hal^4 is a halogen atom such as a chlorine atom] with an organometallic reagent $ArC(R^5)(R^6)MHal^2$ [where M and Hal^2 are as defined above]. The reaction may be carried out as described above for the preparation of intermediates of formula (3).

Where in the general processes described above intermediates such as ArX^1H, and the halides of formulae (6) and (7) are not available commercially or known in the literature, they may be readily obtained from simpler known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other intermediates and in particular compounds of formula (1) where appropriate functional groups exist in these compounds. Particular examples of such methods are given in the Examples hereinafter.

Thus, for example, ester groups such as $-CO_2Alk^4$ in the compounds of formula (1) and intermediates thereto may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the groups R^8 or Alk^4. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an organic solvent e.g. dichloromethane or a mineral acid such as hydrochloric acid in a solvent such as dioxane or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example amides $R^{1a}N(R^2)COAr^2X^1H$ may be obtained by reaction of an amine $R^{1a}N(R^2)H_2$ with an acid HX^1ArCO_2H in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or N,N^1-dicyclohexylcarbodiimide, or a benzotriazole such as [0-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxybenzotriazole such as 1-hydroxybenzotriazole.

The reaction may be performed in the presence of a base, such as an amine e.g. triethylamine or N-methylmorpholine optionally in the presence of a catalytic amount of 4-dimethylaminopyridine in a solvent such as a halogenated hydrocarbon e.g. dichloromethane, at for example ambient temperature.

In a further example, $-OR^{20}$ [where R^{20} represents an alkyl group such as methyl group] in compounds of formula (1) and intermediates thereto may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{20}$ group (where R^{20} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [e.g. $-CO_2Alk^4$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^{20}$ group by coupling with a reagent $R^{20}OH$ in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides for example sodium

triacetoxyborohyride or sodium cyanoborohydride. The reduction may be carried out in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon e.g. toluene and then subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

In a further example, amine [-NH_2] groups in compounds of formula (1) and intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO_2] group may be reduced to an amine [-NH_2], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine (-CH_2NH_2) group may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney® nickel, in a solvent such as an ether e.g. tetrahydrofuran or an alcohol e.g. methanol or ethanol at a temperature from ambient to the reflux temprature, or by chemical reduction using for example a metal hydride e.g. lithium aluminium hydride, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an

electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a group L^1 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

Where desired, imidourea groups, for example $N(R^2)C(=NR^{16})NR^{14}R^{15}$ represented by $R^{1a}N(R^2)$ in compounds of the invention or intermediates thereto may be obtained by reaction of a corresponding amine, for example $-NHR^2$, with a guanidine containing a leaving group, e.g. $LC(=NR^{16})NR^{14}R^{15}$ where L is a leaving group such as a pyrazole group, in a solvent such as acetonitrile at an elevated temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid or m-chloroperoxybenzoic acid in a solvent, e.g. dichloromethane or tert-butanol, at a temperature from the ambient temperature to the reflux temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystalliation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

THF - tetrahydrofuran; Boc - butoxycarbonyl
DMF - dimethyl formamide; DMSO - dimethyl sulphoxide
$Pd(dppf)_2Cl_2$ - dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II)
EDC - 1-(3-dimethylaminopropyl)-3-ethylcarboiimide hydrochloride
DMAP - 4-dimethylaminopyridine

INTERMEDIATE 1

4-[(2-Pyridinylamino)methyl]phenol

4-Hydroxybenzaldehyde (3.9g, 32mmol) and 2-aminopyridine (3.0g, 32mmol) were stirred in toluene (100ml) at room temperature for 5min. After concentrating *in vacuo* the residue was dissolved in ethanol (50ml) and hydrogenated over Pd/C (100mg) under a hydrogen atmosphere, for 18h. The reaction mixture was filtered, concentrated and the crude product was chromatographed (dichloromethane-silica) to yield the title compound as white crystals (3.6g, 56%). ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, m), 7.49 (1H, m), 7.14 (2H, d, J 7.8Hz), 6.79 (2H, d, J 7.8Hz), 6.64 (1H, m), 6.47 (1H, d, J 7.8Hz), 4.79 (1H, br s) and 4.32 (2H, d, J 5.2Hz).

INTERMEDIATE 2

2-Chloro-4-(4-fluorobenzyl)pyrimidine

4-Fluorobenzylbromide (12.7g, 67.1mmol) in THF (35ml) was added to activated zinc (5.2g, 80.5mmol) under nitrogen. After the addition was complete the reaction was refluxed for 15min. After cooling to room temperature the reaction was treated with tetrakis(triphenylphosphine)palladium (0) (2.27g, 2mmol) and 2,4-dichloropyrimidine (10g, 67.1mmol). The reaction was heated under reflux for 1h, then quenched with saturated sodium hydrogen carbonate solution, extracted into dichloromethane, dried over magnesium suphate and concentrated *in vacuo*. Chromatography (dichloromethane-silica) yielded the title compound (15.8g, 88%). ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, d, J 6.5Hz), 7.23 (2H, m), 7.05 (3H, m) and 4.10 (2H, s).

INTERMEDIATE 3

Methyl-3-(2-chloro-4-pyrimidinyl)-3-(4-fluorophenyl)propanoate

Intermediate 2 (5.0g, 22.5mmol) in THF (50ml) was cooled to -78° under nitrogen and treated with sodium bis(trimethylsilyl)amide (1M solution in THF, 24.7ml, 24.7mmol). The reaction was stirred at -78° for 15min, then treated with methyl bromoacetate (3.4g, 22.5mmol) in THF (10ml). After stirring at -78° for 20min the reaction was allowed to warm to room temperature, quenched with water and extracted into ethyl acetate. After drying over magnesium sulphate the filtrate was concentrated *in vacuo* and chromatographed (diisopropylether-silica) to yield the title compound (5.57g, 84%). ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, d, J 5.1Hz), 7.26 (2H, m), 7.06 (1H, d, J 5.1Hz), 6.70 (2H, t, J 8.6Hz), 4.54 (1H, dd, J 8.7, 6.0Hz), 3.62 (3H, s), 3.44 (1H, dd, J 16.7, 8.7Hz) and 2.90 (1H, dd, J 16.7, 6.5Hz).

INTERMEDIATE 4

Methyl-3-[2-(4-cyanoanilino)-4-pyrimidinyl]-3-(4-fluorophenyl) propanoate

Intermediate 3 (4g, 13.58mmol) and 4-aminobenzonitrile (1.6g, 13.58mmol) in DMF (3ml) were heated to 140° for 30min. The reaction mixture was cooled and partitioned between saturated sodium hydrogen carbonate solution and ethyl acetate, the organic phase was separated,

dried over magnesium suphate and concentrated *in vacuo*. The residual black tar was chromatographed (diisopropylether-silica) to yield the title compound as yellow crystals (4.0g, 78%). ^{1}H NMR ($CDCl_3$) δ 8.33 (1H, d, J 3.6Hz), 7.77 (2H, d, J 8.7Hz), 7.61 (2H, d, J 8.7Hz), 7.51 (1H, br s), 7.28 (2H, m), 6.98 (2H, t, J 7.8Hz), 6.69 (1H, d, J 5.2Hz), 4.52 (1H, m), 3.60 (3H, s), 3.41 (1H, dd, J 16.5, 8.7Hz) and 2.91 (1H, dd, J 16.5, 6.9Hz).

INTERMEDIATE 5

Methyl-3-[2-[4-(aminomethyl)anilino]-4-pyrimidinyl)-3-(4-fluoro-phenyl)propanoate

Intermediate 4 (3.85g, 10.2mmol) and para-toluenesulphonic acid (2.0g, 10.2mmol) in methanol (200ml) were hydrogenated over 10% palladium on carbon (100mg) under hydrogen at 50psi. After 24h the reaction was filtered, concentrated and the residue partitioned between ethyl acetate and 10% aqueous sodium hydroxide solution. The organic phase was separated, dried over magnesium suphate, evaporated *in vacuo* and the residue chromatographed (ethyl acetate-silica) to yield the title compound. ^{1}H NMR ($CDCl_3$) δ 8.28 (1H, d, J 6.1Hz), 7.59 (2H, d, J 8.7Hz), 7.29 (4H, m), 7.09 (1H, br s), 7.00 (2H, m), 6.58 (1H, d, J 6.7Hz), 4.48 (1H, m), 3.88 (2H, s), 3.62 (3H, s), 3.42 (1H, dd, J 15.6, 7.8Hz) and 2.91 (1H, dd, J 15.6, 7.8Hz). MS (ES) m/e 381 $[M + H]^+$.

INTERMEDIATE 6

3-[2-[4-(Aminomethyl)anilino]-4-pyrimidinyl)-3-(4-fluorophenyl) propanoic acid

Intermediate 5 (480mg, 1.26mmol) and 0.101M sodium hydroxide (12.48ml, 1.26mmol) in dioxane (2ml) and water (5ml) were heated under reflux for 18h. The dioxane was removed *in vacuo* and the remaining aqueous residue neutralised with 1M hydrochloric acid. After removal of the water *in vacuo* the residue was extracted into methanol, concentrated and washed with water, to yield the title compound (350mg). ^{1}H NMR ($CDCl_3$) δ 9.50 (1H, s), 8.30 (1H, d, J 5.0Hz), 7.69 (2H, d, J 8.5Hz), 7.37 (2H, m), 7.25 (2H, d, J 8.6Hz), 7.10 (2H, t, J 8.9Hz), 6.77 (1H, d, J 5.1Hz), 4.42 (1H, m), 3.73 (2H, s), 3.15 (1H, dd, J 16.0, 8.5Hz) and 2.76 (1H, dd, J 16.3, 6.9Hz). MS (ES) m/e 367 $[M + H]^+$.

INTERMEDIATE 7

2-Chloro-4-(3,5-difluorobenzyl)pyrimidine

The title compound (4.2g, 76%) was prepared from 3,5-dichlorobenzyl-bromide (5.0g, 24.2mmol) and 2,4-dichloropyrimidine (3.6g, 24.2mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.51 (1H, d, J 5.0Hz), 7.04 (1H, d, J 5.0Hz), 6.72 (3H, m) and 4.10 (2H, s). MS (ES) m/e 241 $[M + H]^+$.

INTERMEDIATE 8

Methyl-3-(2-chloro-4-pyrimidinyl)-3-(3,5-difluorophenyl)propanoate

The title compound (4.26g, 82%) was prepared from Intermediate 7 (4.2g, 18.3mmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.49 (1H, d, J 5.2Hz), 7.04 (1H, d, J 5.2Hz), 6.79 (2H, m), 6.62 (1H, m), 4.50 (1H, dd, J 8.6, 6.3Hz), 3.60 (3H, s), 3.39 (1H, dd J 8.6, 6.3Hz), and 2.90 (1H, dd. J 8.6, 6.3Hz). MS (ES) m/e 313 $[M + H]^+$.

INTERMEDIATE 9

Ethyl-4-[(2-chloro-4-pyrimidinyl)methyl]-2-furoate

The title compound (1.65g, 40%)was prepared from 5-(chloromethyl)-2-furan carboxylate (2.84g, 15.1mmol) and 2,4-dichloropyrimidine (2.24g, 15.1mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, d, J 5.5Hz), 7.13 (1H, d, J 5.5Hz), 7.11 (1H, d, J 5.0Hz), 6.34 (1H, d, J 5.0Hz), 4.35 (2H, q, J 7.1Hz) and 4.20 (2H, s). MS (ES) m/e 267 $[M + H]^+$.

INTERMEDIATE 10

***t*-Butyl-3-[5-(ethoxycarbonyl)-3-furyl]-3-(2-chloro-4-pyrimidinyl) propanoate**

The title compound (1.8g, 79%) was prepared from Intermediate 9 (1.6g, 6.0mmol) and *t*-butyl bromoacetate (879µl, 6.0mmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.51 (1H, d, J 6.1Hz), 7.18 (1H, d, J 6.1Hz), 7.09 (1H, d, J 5.5Hz), 6.25 (1H, d, J 5.5Hz), 4.65 (1H, m), 4.32 (2H, m), 3.25 (1H, dd, J 8.6, 6.3Hz) and 2.95 (1H, dd, J 8.6, 6.3Hz), 1.35 (9H, s). MS (ES) m/e 403 $[M + Na]^+$.

INTERMEDIATE 11

t-Butyl-3-(2-chloro-4-pyrimidinyl)-3-[4-fluorophenyl]propanoate

The title compound (4.5g, 80%) was prepared from Intermediate 2 (3.26g, 16.76mmol) in a similar manner to Intermediate 10. ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, d, J 6.0Hz), 7.30-7.21 (2H,m), 7.08-6.97 (3H, m), 4.49 (1H, t, J 8.0Hz), 3.32 (1H, d, J 8.2Hz), 2.84 (1H, d, J 8.2Hz) and 1.35 (9H, s).

INTERMEDIATE 12

Ethyl-3-(2-chloro-4-pyrimidinyl)propanoate

To a stirred solution of zinc bromide (12.39g, 55mmol) in diethyl ether (150ml) at room temperature under a nitrogen atmosphere was added 1-ethoxycyclopropyloxy trimethylsilane (8.72g, 10ml, 50mmol). The reaction mixture was refluxed for 1h. Upon cooling to room temperature THF (300ml) was added. 2,4-Dichloropyrimidine (7.45g, 50mmol) was added as a solution in THF (100ml), followed by tetrakis(triphenylphosphine) palladium (0) (1.156g, 1.0mmol) as a solution in THF (50ml). The reaction mixture was heated under reflux for 3h. Upon cooling, the reaction mixture was partitioned between saturated sodium bicarbonate solution (500ml) and dichloromethane (500ml). The aqueous layer was further washed with dichloromethane (100ml) and the combined organic fractions dried over magnesium sulphate, filtered and the solvent removed by evaporation *in vacuo*. The title compound was isolated after purification by flash column chromatography (1:1 diethyl ether, hexane-silica) as a colourless oil (7.83g, 73%); ^{1}H NMR ($CDCl_3$) δ 8.49 (1H, d, J 5.0Hz), 7.18 (1H, d, J 5.0Hz), 4.13 (2H, q, J 7.0Hz), 3.09 (2H, t, J 7.0Hz), 2.83 (2H, t, J 7.0Hz) and 1.25 (3H, t, J 7.0Hz).

INTERMEDIATE 13

Ethyl-3-(2-[4-{(2-pyridinylamino)methyl}phenoxy]-4-pyrimidinyl) propanoate

To a stirred solution of Intermediate 1 (1.0g, 5mmol) in THF (20ml) was added in a single portion sodium hydride (60% dispersion in mineral oil, 0.2g, 5mmol). The reaction mixture was stirred for 30min at room temperature. Intermediate 12 (1.07g, 5mmol) was added as a solution in THF (10ml). The reaction mixture was heated to reflux for 3h. Upon cooling the reaction mixture was poured onto saturated sodium bicarbonate solution (50ml) and extracted twice with dichloromethane

(50ml). The combined organic fractions were dried over magnesium sulphate, filtered and the solvent removed by evaporation *in vacuo*. Purification was by flash column chromatography (diethyl ether-silica) giving the title compound (0.95g, 50%). ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d, J 5.0Hz), 8.16-8.10 (1H, m), 7.48-7.39 (3H, m), 7.20-7.15 (2H, m), 6.93 (1H, d, J 5.0Hz), 6.61 (1H, dd, J 6.5, 1.0Hz), 6.42 (1H, d, J 6.0Hz), 4.92 (1H, br s), 4.58 (2H, d, J 6.0Hz), 4.12 (2H, q, J 8.0Hz), 3.08 (2H, t, J 8.0Hz), 2.54 (2H, t, J 8.0Hz) and 1.27 (3H, t, J 8.0Hz).

INTERMEDIATE 14

Ethyl-3-(2-chloro-4-pyrimidinyl)propenoate

To a stirred solution of borane dimethyl sulphide complex (1.42ml, 15mmol) in THF at 0° was added dropwise α-pinene (5ml, 31.5mmol). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to -35° and ethyl propiolate (1.47g, 1.52ml, 15mmol) added dropwise. The reaction mixture was stirred at room temperature for 2h and then cooled to 0°. Acetaldehyde (5ml, 3.94g, 89mmol) was added dropwise. The reaction mixture was heated to reflux for 1h. Upon cooling the solvent and volatiles were removed by evaporation *in vacuo*. The residue was dissolved in THF (50ml) and pinacol (1.8g, 18mmol) added. The reaction mixture was stirred for 1h at room temperature. The solvent and volatiles were removed by evaporation *in vacuo*. To the crude product was added 2,4-dichloropyrimidine (2.24g, 15mmol) followed by cesium fluoride (4.56g, 30mmol) and tetrakis(triphenylphosphine)palladium (0) (0.88g, 0.75mmol). The reaction mixture was diluted with dioxane (50ml) and heated under reflux for 3h. Upon cooling the reaction mixture was poured into saturated sodium hydrogen carbonate solution (100ml) and extracted twice with dichloromethane (100ml). The combined organic fractions were dried over magnesium sulphate, filtered and the solvent removed by evaporation *in vacuo*. Purification by flash column chromatography (diisopropylether-silica) gave the title compound (1.59g, 50%). ^{1}H NMR ($CDCl_3$) δ 6.78 (1H, d, J 12Hz), 6.62 (1H, d, J 12Hz), 4.22 (2H, q, J 8Hz) and 1.21 (3H, t, J 8Hz).

INTERMEDIATE 15

Ethyl-3-(2-[-((2-pyridinylamino)methyl)phenoxy]-4-pyrimidinyl) propenoate

To a stirred solution of Intermediate 14 (0.17g, 0.8mmol) and Intermediate 1 (0.18g. 0.9mmol) in DMF (5ml) was added in a single portion cesium carbonate (0.167g, 0.5mmol) the reaction mixture was heated under reflux for 4h. Upon cooling the reaction mixture was poured onto saturated sodium hydrogen carbonate solution (2.0ml) and the product extracted twice with dichloromethane (20ml). The combined organic fractions were dried over magnesium sulphate, filtered and the solvent removed by evaporation *in vacuo*. Purification by flash column chromatography (diethyl ether -silica) gave the title compound (0.02g, 7%). ^{1}H NMR ($CDCl_3$) δ 8.59 (1H, d, J 6Hz), 8.08 (1H, br s), 7.49 (1H, d, J 16Hz), 7.43 (2H, d, J 8Hz), 7.52-7.4 (1H, m), 7.19 (2H, d, J 8Hz), 7.07 (1H, d, J 6Hz), 7.01 (1H, d, J 16Hz), 6.62 (1H, br t, J 8Hz), 6.45 (1H, br d, J 6Hz), 4.55 (2H, br d, J 6Hz), 4.29 (2H, q, J 8Hz) and 1.31 (3H, t, J 8Hz).

INTERMEDIATE 16

2-Chloro-4-(4-cyanobenzyl)pyrimidine

The title compound (1.5g, 32%) was prepared from *p*-cyanobenzyl bromide (4.0g, 2.04mmol) in a similar manner to Intermediate 2 and used crude in the next step.

INTERMEDIATE 17

***t*-Butyl-3-(2-chloro-4-pyrimidinyl)-3-(4-cyanophenyl)propanoate**

The title compound (1.6g, 72%) was prepared from Intermediate 16 (1.5g, 6.5mmol) in a similar manner to Intermediate 10. ^{1}H NMR ($CDCl_3$) δ 8.49 (1H, d, J 5.2Hz), 7.61 (2H, d, J 8.2Hz), 7.42 (2H, d, J 8.2Hz), 7.08 (1H, d, J 5.2Hz), 4.53 (1H, t, J 7.2Hz), 3.35 (1H, dd, J 17, 8.2Hz), 2.88 (1H, dd, J 17, 7.2Hz) and 1.38 (9H, s). MS (ES) m/e 344 $[M + H]^+$.

INTERMEDIATE 18

4-(Benzyloxy)-*N*'-(2-pyridinyl)benzamide

4-Benzyloxybenzoic acid (1.0g, 4.38mmol) was stirred overnight in dichloromethane (200ml) with EDC (640mg, 5.25mmol) DMAP (2.44mg, 2mmol), 2-aminopyridine (412.2mg, 4.38mmol) and N-methyl morpholine (1ml, 9mmol). After this time the reaction was partitioned between

dichloromethane (200ml) and saturated sodium bicarbonate solution (200ml) and the organics dried over magnesium sulphate. The solvents were removed *in vacuo* and the crude oil columned (ethyl acetate-silica) to yield the title compound (370mg, 28%). ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, J 8.5Hz), 8.30 (1H, d, J 8.2Hz), 7.99 (2H, d, J 8.7Hz), 7.84 (1H, dd, J 15.8, 7.2Hz), 7.48-7.35 (5H, m), 7.16-7.02 (3H,m), 5.14 (2H, s). MS (ES) m/e 305 $[M + H]^+$.

INTERMEDIATE 19

4-Hydroxy-*N'*-(2-pyridinyl)benzamide

Intermediate 18 (370mg, 1.21mmol) was dissolved in ethanol (100ml) and 10% palladium on carbon (1g) added. The mixture was stirred under a hydrogen atmosphere for 5h at room temeprature. After this time the mixture was filtered through Celite®, and the plug was washed with dichloromethane (2 x 100ml). The combined washings were concentrated *in vacuo* to give the title compound (220mg, 85%). ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, d, J 8.5Hz), 7.86-7.75 (3H, m), 7.20-7.01 (1H, m), 6.95-6.81 (2H, m). MS (ES) m/e 215 $[M + H]^+$.

INTERMEDIATE 20

***t*-Butyl-3-(4-fluorophenyl)-3-(2-[4-cyanophenoxy]-4-pyrimidinyl) propanoate**

The title compound (5.1g, 81%) was prepared from 4-cyanophenol (1.77g, 14.9mmol) and Intermediate 11 (5.0g, 14.8mmol)in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d, J 8.6Hz), 7.58 (2H, d, J 9.2Hz), 7.42 (2H, d, J 9.2Hz), 7.22-7.12 (2H, m), 6.98-6.89 (3H, m), 4.48-4.40 (1H, m), 3.38-3.25 (1H, m), 2.88-2.71 (1H, m) and 1.29 (9H, s). MS (ES) m/e 420 $[M + H]^+$.

INTERMEDIATE 21

***t*-Butyl-3-(2-[4-aminomethylphenoxy]4-pyrimidinyl)-3-(4-fluorophenyl)propanoate**

Raney® nickel (1g) was washed with water (3 x 100ml) and ethanol (2 x 100ml). The metal was suspended in ethanol (150ml) and concentrated ammonia solution (4ml) and Intermediate 20 (5.1g, 12.1mmol) in ethanol (10ml) added. The mixture was rapidly stirred under a hydrogen

atmosphere for 3h. The solution was filtered through Celite® and the plug washed with dichloromethane (3 x 100ml). The solvent was removed *in vacuo* to yield the title compound as a yellow gum (4.4g, 85%). ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, d, J 5.8Hz), 7.41 (2H, d, J 8.6Hz), 7.28-7.22 (2H, m), 7.12 (2H, d, J 8.6Hz), 6.98-6.85 (2H, m), 6.68 (1H, d, J 5.8Hz), 4.41 (1H, t, J 7.8Hz), 3.98 (2H, s), 3.25-3.18 (1H, m), 2.82-2.68 (1H, m) and 1.28 (9H, s). MS (ES) m/e 424 $[M + H]^+$.

INTERMEDIATE 22

***t*-Butyl-3-[2-[4-[(4-nitro-2-pyridinyl)amino]methyl]phenoxy]-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate**

The title compound (5.70g, 70%) was prepared from Intermediate 21 (634mg, 1.49mmol) potassium carbonate (205mg, 1.49mmol) and 2-chloro-4-nitropyridine (237mg, 1.49mmol) in a similar manner to Intermediate 15. ^{1}H NMR ($CDCl_3$) δ 9.10 (1H, s), 8.32 (1H, d, J 5.2Hz), 8.19 (1H, d, J 8.2Hz), 7.41 (2H, d, J 8.1Hz), 7.20-7.15 (4H, m), 7.07-6.85 (3H, m), 6.41 (1H, d, J 8.4Hz), 4.69 (2H, s), 4.42 (1H, t, J 7.2Hz), 3.21 (1H, dd, J 15.2, 8.1Hz), 2.81 (1H, dd, J 15.3, 7.9Hz) and 1.31 (9H, s). M/S (ES) m/e 546 $[M + H]^+$.

INTERMEDIATE 23

***t*-Butyl-3-[2-[4-[[(4-amino-2-pyridinyl]amino]methyl]phenoxy]-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate**

Intermediate 22 (450mg, 0.82mmol) in ethanol (100ml) was stirred with 10% palladium on carbon (1g) under an atmosphere of hydrogen for 1h. The solution was filtered through a plug of Celite® and concentrated *in vacuo* to give the title compound as a red gum (422mg, 100%). ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, d, J 5.2Hz), 7.60 (1H, s), 7.41 (2H, d, J 8.3Hz), 7.28-7.19 (2H, m), 7.15 (2H, d, J 8.1Hz), 7.10 (1H, d, J 7.2Hz), 6.92-6.89 (2H, m), 6.81 (1H, d, J 5.2Hz), 6.39 (1H, d, J 7.2Hz), 4.49 (2H, s), 4.42 (1H, t, J 7.2Hz), 3.21 (1H, dd, J 15.3Hz, 8.1Hz), 2.78 (1H, dd, J 15.3, 7.9Hz), 1.31 (9H, s). MS (ES) m/e 516 $[M + H]^+$.

INTERMEDIATE 24

***t*-Butyl-3-[2-[4-[(1*H*-1,3-benzimidazol-2-yl-amino)methyl]phenoxy]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoate**

1,1-Thiocarbonyl diimidazole (629mg, 3.54mmol), imidazole (48mg, 0.7mmol) and Intermediate 21 (1.0g, 2.36mmol) were stirred at 0° in acetonitrile (100ml) for 1h then warmed to room temperature and stirred for 3h. Phenylenediamine (509mg, 4.72mmol) was added and the mixture was stirred at 50° for 3h. After this time the mixture was stirred at ambient temperature overnight. At this point the solvents were removed *in vacuo* and the crude foam heated in ethanol (100ml) with red mercuric oxide (368mg, 1.7mmol) and sulphur (3mg, 0.087mmol) at reflux overnight. The mixture was cooled, filtered and the solvent removed *in vacuo*. The crude gum was subjected to column chromatography (ethyl acetate-silica) to yield the title compound as cream foam (550mg, 43%). ^{1}H NMR ($CDCl_3$) δ 8.20 (1H, d, J 5.2Hz), 7.45-7.10 (8H, m), 7.12-6.82 (4H, m), 6.81-6.72 (1H, d, J 5.2Hz), 4.70-4.62 (2H, m), 4.41 (1H, t, J 7.2Hz), 3.12 (1H, dd, J 16.1, 7.1Hz), 2.65 (1H, dd, J 15.8, 7.2Hz) and 1.38 (9H, s). MS (ES) m/e 541 $[M + H]^+$.

INTERMEDIATE 25

t-Butyl-3-[2-(4-cyanobenzyl)-4-pyrimidinyl]-3-(4-fluorophenyl) propanoate

Activated zinc (507mg, 7.8mmol) was suspended in THF (5ml) and 4-cyanobenzylbromide (1.27g, 6.5mmol) in THF (5ml) was added and the mixture refluxed for 30min. Tetrakis(triphenylphosphine) palladium (0) (200mg) and Intermediate 11 (2.19g, 6.5mmol) in THF (10ml) were added and the mixture refluxed for 3h. After cooling the mixture was partitioned between ethyl acetate (100ml) and 10% ammonium chloride solution (100ml) and the organics dried over magnesium sulphate. The solvent was removed *in vacuo* and the crude solid subjected to column chromatography (diisopropyl ether —> ethyl acetate-silica) to yield the title compound as a yellow oil (2.2g, 81%). ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, d, J 5.2Hz), 7.58 (2H, d, J 8.6Hz), 7.42 (2H, d, J 8.6Hz), 7.20-7.12 (2H, m), 6.99-6.87 (3H, m), 4.48-4.40 (1H, m), 4.36 (2H, s), 3.27 (1H, dd, J 16.2, 8.9Hz), 2.81 (1H, dd, J 16.2, 8.5Hz) and 1.28 (9H, s). MS (ES) m/e 418 $[M + H]^+$.

INTERMEDIATE 26

t-Butyl-3-(2-[4-(aminomethyl)benzyl]-4-pyrimidinyl)-3-(4-fluorophenyl) propanoate

The title compound (1.4g, 64%) was prepared from Intermediate 25 (2.2g, 5.2mmol) in a similar manner to Intermediate 21. ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, d, J 5.2Hz), 7.32 (2H, d, J 8.2Hz), 7.22-7.15 (4H, m), 6.98-6.85 (3H, m), 4.42 (1H, t, J 8.4Hz), 4.25 (2H, s), 3.79 (2H, s), 3.3 (1H, dd, J 16.2, 8.4Hz), 3.32 (1H, dd, J 16.2, 8.4Hz) and 1.28 (9H, s). MS (ES) m/e 422 $[M + H]^+$.

INTERMEDIATE 27

t-Butyl-3-(2-[4-([[*N,N'*-bis-boc((amino)imino)methyl]amino]methyl) phenoxy]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoate

Intermediate 21 (200mg, 0.49mmol), *N,N'*-bis-boc-guanyl triflate (192mg, 0.46mmol) and triethylamine (70.7ml, 0.49mmol) were stirred in dichloromethane (10ml) fo 12h. The organics were then washed with saturated sodium bicarbonate solution (20ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to yield a white foam (300mg, 92%). ^{1}H NMR ($CDCl_3$) δ 8.68-8.61 (1H, br m), 8.38 (1H, d, J 5.2Hz), 7.38 (2H, d, J 8.6Hz), 7.29-7.21 (2H, m), 7.18 (2H, d, J 8.6Hz), 7.13-6.92 (2H, m), 6.82 (1H, d, J 5.2Hz), 4.62 (2H, d, J 5.4Hz), 4.43 (1H, t, J 7.4Hz), 3.25 (1H, dd, J 16.5, 7.4Hz), 2.78 (1H, dd, J 10.5, 7.4Hz), 1.58 (9H, s), 1.59 (9H, s) and 1.28 (9H, s). MS (ES) m/e 665 $[M + H]^+$.

INTERMEDIATE 28

2-Ethoxyethyl-3-(2-[4-cyanoanilino]-4-pyrimidinyl)-3-(4-fluorophenyl) propanoate

4-Amino-benzonitrile (1.58g, 13.37mmol) and Intermediate 11 (4.5g, 13.37mmol) were dissolved in ethoxyethanol (50ml) and the reaction mixture was heated under reflux for 3h. Upon cooling the reaction mixture was poured into saturated sodium hydrogen carbonate solution (10ml) and the product extracted twice with dichloromethane (100ml). The combined organic fractions were dried over magnesium sulphate, filtered and the solvent removed by evaporation *in vacuo*. Purification by flash column chromatography (2:1 diethyl ether, hexane-silica) gave the title compound (3.2g, 55%). ^{1}H NMR ($CDCl_3$) δ 8.31 (1H, d, J 6.0Hz), 7.78 (2H, d, J 10.0Hz), 7.62 (2H, d, J 10.0Hz), 7.58 (1H, br s), 7.23 (2H, t, J 8.0Hz), 7.02

(2H, t, J 8.0Hz), 6.66 (1H, d, J 6.0Hz), 4.53 (1H, dd, J 8.0, 2.0Hz), 4.28-4.12 (2H, m), 3.60-3.53 (2H, m), 3.48 (2H, q, J 8.0Hz), 3.43 (1H, dd, J 16.0, 8.0Hz), 2.92 (1H, dd, J 18.0, 8.0Hz) and 1.21 (3H, t, J 8.0Hz).

INTERMEDIATE 29

2-Ethoxyethyl-3-[2-[4-(aminomethyl)anilino]-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate

The title compound (1.05g, 32%), purified by flash chromatography (20% methanol, 80% dichloromethane, silica) was prepared from Intermediate 28 (3.2g, 7.35mmol) in a similar manner to Intermediate 21. ^{1}H NMR ($CDCl_3$) δ 8.23 (1H, d, J 5.0Hz), 7.58 (2H, d, J 8.0Hz), 7.35-7.20 (5H, m), 6.99 (2H, t, J 9.0Hz), 6.52 (1H, d, J 5.0Hz), 4.50-4.42 (1H, m), 4.17 (2H, t, J 5.0Hz), 3.60-3.38 (5H, m), 2.92 (1H, dd, J 16.0, 7.0Hz) and 1.18 (3H, t, J 7.0Hz). MS (ES) m/e 439 $[M+H]^+$.

INTERMEDIATE 30

2-Ethoxyethyl-3-(4-fluorophenyl)-3-(2-[4-((2-pyridinylamino)methyl)anilino]-4-pyrimidinyl)propanoate

A stirred solution of the compound of Intermediate 29 (0.438g, 1.0mmol) in 2-fluoropyridine (10ml) was heated to reflux for 4h. Upon cooling the reaction mixture was poured onto saturated sodium hydrogen carbonate solution (50ml) and extracted twice with dichloromethane (50ml). The combined organic fractions were dried over magnesium sulphate, filtered and the solvent removed by evaporation *in vacuo*. Purification by flash column chromatography (diethyl ether-silica) gave the title compound (0.18g, 38%). ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, d, J 6.0Hz), 8.12 (1H, d, J 4.0Hz), 7.62 (1H, br s), 7.58 (2H, d, J 8.0Hz), 7.42 (1H, t, J 7.0Hz), 7.33 (2H, d, J 8.0Hz), 7.31-7.22 (2H, m), 6.99 (1H, t, J 9.0Hz), 6.59 (1H, dd, J 8.0, 1.0Hz), 6.53 (1H, d, J 6.0Hz), 6.39 (1H, d, J 9.0Hz), 5.12 (1H, br s), 4.50-4.43 (3H, m), 4.18 (2H, t, J 6.0Hz), 3.58-3.36 (5H, m), 2.93 (1H, dd, J 16.0, 8.0Hz) and 1.18 (3H, t, J 7.0Hz).

INTERMEDIATE 31

2-Chloro-4-benzyl pyrimidine

The title compound (quantitiative yield) was prepared from benzyl bromide (1.71g, 1.19ml, 10mmol) and 2,4-dichloropyrimidine (1.49g, 10mmol) in a similar manner to Intermediate 2, and was used without purification.

INTERMEDIATE 32

***t*-Butyl-3-(2-chloro-4-pyrimidinyl)-3-phenyl propanoate**

The title compound (3.9g, 97%) was prepared from Intermediate 31 (2.70g, 12.5mmol) in a similar manner to Intermediate 10. ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d, J 5.2Hz), 7.35-7.15 (5H, m), 7.54 (1H, d, J 5.2Hz), 4.58-4.42 (1H, m), 3.28 (1H, dd, J 16.4, 8.1Hz), 2.85 (1H, dd, J 16.4, 7.5Hz) and 1.38 (9H, s). MS (ES) m/e 319 $[M + H]^+$.

INTERMEDIATE 33

***t*-Butyl-3-phenyl-3-(2-[4-((2-pyridinylamino)methyl)phenoxy]-4-pyrimidinyl)propanoate**

The title compound (1.2g, 49%) was prepared from Intermediate 1 (1.00g, 5mmol) and Intermediate 32 (1.59g, 5mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.34 (1H, d, J 5.2Hz), 7.48-7.39 (3H, m), 7.35-7.12 (7H, m), 6.87 (1H, d, J 5.2Hz), 6.63-6.56 (1H, m), 6.39 (1H, d, J 8.2Hz), 4.90 (1H, bs), 4.55 (2H, d, J 8.1Hz), 4.45 (1H, t, J 8.2Hz), 3.31 (1H, dd, J 16.2, 8.1Hz), 2.78 (1H, dd, J 16.1, 7.9Hz) and 1.30 (9H, s). MS (ES) m/e 483 $[M + H]^+$.

INTERMEDIATE 34

Methyl-4-[(2-Chloro-4-pyrimidinyl)methyl]-4-benzoate

The title compound (4.35g, 63%) was prepared from methyl (4-bromomethyl)benzoate (5.0g, 21.8mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.51 (1H, d, J 5.1Hz), 8.03 (2H, d, J 8.4Hz), 7.35 (2H, d, J 8.3Hz), 7.03 (1H, d, J 5.1Hz), 4.15 (2H, s) and 3.91 (3H, s). MS (ES) m/e 263 $[M+H]^+$.

INTERMEDIATE 35

***t*-Butyl-3-(2-chloro-4-pyrimidinyl)-3-[4-(methoxycarbonyl)phenyl] propanoate**

The title compound (4.34g, 69%) was prepared from Intermediate 34 (4.36g, 16.6mmol) in a similar manner to Intermediate 10. ^{1}H NMR

($CDCl_3$) δ 8.41 (1H, d, J 6.2Hz), 7.95 (2H, d, J 8.6Hz), 7.05 (2H, d, J 8.6Hz), 7.12 (1H, d, J 6.2Hz), 4.57 (1H, t, J 7.8Hz), 3.87 (3H, s), 3.48-3.32 (1H, m), 2.91-2.81 (1H, m) and 1.29 (9H, s). MS (ES) m/e 378 $[M+H]^+$.

INTERMEDIATE 36

***t*-Butyl-3-[4-(methoxycarbonyl)phenyl]-3-(2-{4-[(2-pyridinylamino) methyl]phenoxy}-4-pyrimidinyl)propanoate**

The title compound (350mg, 27%) was prepared from Intermediate 1 (500mg, 2.5mmol) and Intermediate 35 (941mg, 2.5mmol) in a similar manner to Intermediate 13. ^1H NMR ($CDCl_3$) δ 8.38 (1H, d, J 6.4Hz), 8.10 (1H, d, J 5.2Hz), 7.89 (2H, d, J 8.6Hz), 7.48-7.30 (5H, m), 6.59 (1H, t, J 5.2Hz), 6.43 (1H, d, J 6.4Hz), 4.59 (2H, d, J 5.2Hz), 4.47 (1H, t, J 5.2Hz), 3.80 (3H, s), 3.31-3.28 (1H, m), 2.91-2.72 (1H, m) and 1.28 (9H, 2). MS (ES) m/e 541 $[M + H]^+$.

INTERMEDIATE 37

***t*-Butyl-3-{[*N'*-butoxycarbonyl(2-aminoethyl)]4-benzamide}-3-(2-[4-{(2-pyridinylamino)methyl}phenoxy]-4-pyrimidinyl)propanoate**

The compound of Example 19 (1.0g, 1.9mmol) in DMF (70ml) was treated with *N*-bocethylenediamine (0.5g, 2.9mmol), diisopropylethylamine (0.37g, 2.9mmol), EDC (0.55g, 2.9mmol), 1-hydroxy-7-azabenzatriazole (0.39g, 2.9mmol) and stirred at room temperature overnight. Water was then added to the reaction and the mixture extracted into ethyl acetate. The organic layer was dried over magnesium sulphate and reduced *in vacuo* to an orange gum (1.1g, 86%). ^1H NMR ($CDCl_3$) δ 8.36 (1H, d, J 5.1Hz), 8.19 (1H, m), 8.02 (1H, s), 7.70 (2H, d, J 8.4Hz), 7.42 (3H, m), 7.30 (2H, d, J 8.2Hz), 7.12 (2H, d, J 8.4Hz), 6.85 (1H, d, J 5.1Hz), 6.59 (1H, m), 6.41 (1H, d, J 8.4Hz), 5.02 (1H, br m), 4.55 (2H, d, J 5.8Hz), 4.47 (1H, m), 3.53 (2H, m), 3.43 (2H, m), 3.20 (1H, dd, J 8.6, 6.7Hz), 2.82 (1H, dd, J 7.0, 6.3Hz), 1.42 (9H, s) and 1.32 (9H, s). MS (ES) m/e 669 $[M + H]^+$.

INTERMEDIATE 38

***t*-Butyl-3-[2-(4-cyano-*N*-methylanilino)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate**

A mixture of 4-(*N*-methylamino)benzonitrile (1.18g, 8.92mmol) Intermediate 11 (2.0g, 5.96mmol) sodium *t*-butoxide (856mg, 8.92mmol)

and Pd $(dppf)_2Cl_2$ (212mg, 0.29mmol) in THF (12ml) were stirred at 80° for 8h. The reaction was cooled, quenched with water and extracted into dichloromethane, dried over sodium sulphate and evaporated *in vacuo*. Purification by flash chromatography (4:1→3:2 hexane, diethyl ether-silica) gave the title compound (2.2g, 85%) ^{1}H NMR ($CDCl_3$) δ 8.20 (1H, d, J 5.0Hz), 7.61 (2H, d, J 8.6Hz), 7.46 (2H, d, J 8.6Hz), 7.20 (2H, dd, J 8.6, 5.4Hz), 6.94 (2H, t, J 8.6Hz), 6.54 (1H, d, J 5.0Hz), 4.33 (1H, dd, J 8.7, 6.9Hz), 3.60 (3H, s), 3.17 (1H, dd, J 15.9, 8.7Hz), 2.72 (1H, dd, J 15.9, 6.9Hz) and 1.29 (9H, s). MS (ES) m/e 433 $[M + H]^+$.

INTERMEDIATE 39

***t*-Butyl-3-[2-(4-aminomethyl-*N*-methylanilino)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate**

The title compound (1.6g, 72%) was prepared from Intermediate 38 (2.2g, 5.04mmol) in a similar manner to Intermediate 21. ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, d, J 5.0Hz), 7.35 (2H, d, J 8.3Hz), 7.28-7.20 (4H, m), 6.96 (2H, t, J 8.7Hz), 6.39 (1H, d, J 5.0Hz), 4.30 (1H, dd, J 8.4, 7.3Hz), 3.90 (2H, s), 3.55 (3H, s), 3.21 (1H, dd, J 15.9, 8.4Hz), 2.75 (1H, dd, J 15.9, 7.3Hz) and 1.31 (9H, s). MS (ES) m/e 437 $[M + H]^+$.

INTERMEDIATE 40

***t*-Butyl-3-[2-(4-(*N,N'*-bis-boc-({amino(imino)methyl}amino)methyl)-*N*-methylanilino)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate**

The title compound (825mg, 68%) was prepared from Intermediate 39 (800mg, 1.8mmol) in a similar manner to Intermediate 27. ^{1}H NMR ($CDCl_3$) δ 8.63 (1H, br s), 8.16 (1H, dd, J 5.0Hz), 7.46-7.23 (6H, m), 6.96 (2H, t, J 8.2Hz), 6.42 (1H, d, J 5.0Hz), 4.65 (2H, d, J 5.1Hz), 4.30 (1H, dd, J 8.5, 7.1Hz), 3.56 (3H, s), 3.20 (1H, dd, J 15.9, 8.5Hz), 2.75 (1H, dd, J 15.9,7.1Hz),1.53 (9H, s), 1.49 (9H, s) and 1.31 (9H, s). MS (ES) m/e 679 $[M + H]^+$.

INTERMEDIATE 41

***t*-Butyl-3-[2-[4-(aminomethyl)phenoxy]-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate**

The title compound (1.3g, 38%) was prepared from 4-hydroxybenzylamine (1.0g, 8.14mmol) and Intermediate 11 (2.7g, 8.14mmol) in a similar

manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.13 (1H, d, J 5.2Hz), 7.54 (2H, d, J 7.8Hz), 7.24 (2H, dd, J 7.8, 6.9Hz), 7.09 (2H, d, J 7.8Hz), 6.99 (2H, t, J 7.8Hz), 6.81 (1H, d, J 5.2Hz), 4.43 (1H, t, J 6.9Hz), 4.09 (2H, br s), 3.23 (1H, dd, J 16.5, 7.8Hz), 2.79 (1H, dd, J 16.5, 6.9Hz) and 1.29 (9H, s).

INTERMEDIATE 42

t-Butyl-3-(4-fluorophenyl)-2-(2-{4-[(3,4,5,6-tetrahydro-2*H*-azepin-7-ylamino)methyl]phenoxy}-4-pyrimidinyl)propanoate

Intermediate 41 (250mg, 0.59mmol) in acetonitrile (2ml) was treated with 1-aza-methoxy-1-cycloheptene (75mg, 0.59mmol) and heated under reflux overnight. The solvent was removed *in vacuo* and the residue crystallised from diisopropylether, further purification by reverse phase chromatography (70% ethanol, 30%water-reverse phase silica) yielded the title compound (200mg). ^{1}H NMR (d^6 DMSO) δ 10.35 (1H, br s), 8.53 (1H, d, J 5.0Hz), 7.63 (1H, d, J 8.5Hz), 7.44 (1H, dd, J 8.7, 5.5Hz), 7.29 (1H, d, J 5.0Hz), 7.24-7.14 (4H, m), 4.76 (2H, s), 4.58 (1H, t, J 7.1Hz), 3.60-3.57 (2H, m), 3.22 (1H, dd J 15.9, 8.8Hz), 2.98-2.83 (3H, m), 1.82-1.69 (4H, br m), 1.69-1.59 (2H, br m) and 1.30 (9H, s).

INTERMEDIATE 43

4-Benzyloxybenzylalcohol

4-Benzyloxybenzaldehyde (5g, 23.6mmol) in ethanol (50ml) was treated with sodium borohydride (450mg, 11.8mmol) and stirred at room temperature for 1h. The reaction was quenched with 10% hydrochloric acid, the ethanol removed *in vacuo* and the aqueous residue extracted into dichloromethane, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (dichloromethane-silica) yielded the title compound (5.1g). ^{1}H NMR ($CDCl_3$) δ 7.48-7.25 (7H, m), 6.98 (2H, d, J 8.5Hz), 5.10 (2H, s) and 4.52 (2H, s).

INTERMEDIATE 44

4-Benzyloxybenzylchloride

Intermediate 43 (1g, 4.67mmol) in dichloromethane (5ml) was treated with thionyl chloride (0.34ml, 4.59mmol) and stirred at room temperature for 20min. The reaction was concentrated *in vacuo* yielding the title

compound (1.0g). ^{1}H NMR ($CDCl_3$) δ 7.45-7.32 (5H, m), 7.31 (2H, d, J 8.5Hz), 6.98 (2H, d, J 8.5Hz), 5.09 (2H, s) and 4.59 (2H, s).

INTERMEDIATE 45

1-(4-Benzyloxyphenylmethyl)-1*H*-imidazole

Intermediate 44 (1g, 4.67mmol) in DMF (10ml) was treated with imidazole (635mg, 9.34mmol) and stirred at room temperature 2h then heated under reflux for 1h. The solvent was removed *in vacuo* and the residue partitioned between water and dichloromethane, the organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo*. The resulting oil was chromatographed (94% ethyl acetate, 5% methanol, 1% triethylamine-silica) yielding the title compound (0.8g, 65%). ^{1}H NMR ($CDCl_3$) δ 7.53 (1H, s), 7.46-7.30 (5H, m), 7.10 (3H, m), 6.96 (2H, d, J 8.5Hz), 6.89 (1H, s), 5.08 (2H, s) and 5.03 (2H, s).

INTERMEDIATE 46

1-(4-Hydroxyphenylmethyl)-1*H*-imidazole

Intermediate 45 (750mg, 2.84mmol) in THF (20ml), ethanol (2ml) and water (2ml) was treated with hydrochloric acid (0.3ml) and was hydrogenated at atmospheric pressure over 10% palladium on carbon (100mg). After 2h the catalyst was removed by filtration and the filtrate concentrated *in vacuo* yielding the title compound (545mg). ^{1}H NMR ($CDCl_3$) δ 8.7 (1H, s), 7.24 (1H,s), 7.16 (1H, s), 7.08 (2H, d, J 8.5Hz), 6.72 (2H, d, J 8.5Hz) and 5.14 (2H, s).

INTERMEDIATE 47

***t*-Butyl-3-(4-fluorophenyl)-3-[2-[4-(1-*H*-imidazol-1-ylmethyl)phenoxy]-4-pyrimidinyl]propanoate**

The title compound (0.8g, 54%) was prepared from Intermediate 46 (545mg, 3.13mmol) and Intermediate 11 (1.05g, 3.13mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.1Hz), 7.60 (1H, s), 7.25-7.14 (6H, m), 7.12 (1H, s), 6.99 (3H, m), 6.88 (1H, d, J 5.1Hz), 5.18 (2H, s), 4.48 (1H, t, J 7.0Hz), 3.24 (1H, dd, J 16.6, 8.5Hz), 2.80 (1H, dd, J 16.5, 7.0Hz) and 1.34 (9H, s).

INTERMEDIATE 48

t-Butyl-3-(2-(4-[(4,5-dihydro-1*H*-imidazol-2-ylamino)methyl]phenoxy)-4-pyrimidinyl)-3-(4-fluorophenyl)propanoate

Intermediate 41 (350mg, 0.83mmol), 2-thiomethylimidazolinium iodide (187mg, 0.8mmol) and diisopropylethylamine (92mg, 0.8mmol) were dissolved in dioxane (5ml) and heated under reflux 1h. The solvent was removed *in vacuo* and the residue partitioned between saturated sodium hydrogen carbonate solution and dichloromethane, the organic phase was separated, dried over magnesium sulphate and concentrated yielding the title compound (275mg). ^{1}H NMR ($CDCl_3$) δ 8.34 (1H, d, J 5.2Hz), 7.42 (2H, d, J 8.7Hz), 7.23 (2H, dd, J 7.8, 6.9Hz), 7.19 (2H, d, J 8.7Hz), 7.00 (2H, t, J 7.8Hz), 6.95 (1H, d, J 5.2Hz), 4.51 (2H, s), 4.44 (1H, t, J 6.4Hz), 3.63 (4H, br s), 3.21 (1H, dd, J 16.5, 7.8Hz), 2.80 (1H, dd, J 16.5, 7.0Hz) and 1.33 (9H, s).

INTERMEDIATE 49

1-(4-Benzyloxybenzyl)-1,2,4-triazine

Intermediate 43 (1.0g, 4.7mmol) in dichloromethane (10ml) was treated with thionyl chloride (750mg, 6.3mmol) and stirred for 30min. The solvent was removed *in vacuo*. 1,2,4-Triazole (810mg, 11.7mmol) was added to sodium hydride (60% dispersion in mineral oil, 470mg, 11.7mmol) in DMF and stirred at room temperature for 15min. Intermediate 44 was added and the reaction stirred for 1h before the solvent was removed *in vacuo* and the residue partitioned between saturated sodium hydrogen carbonate and dichloromethane. The organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (98% dichloromethane, 2% methanol-silica) yielded the title compound (1.3g). ^{1}H NMR ($CDCl_3$) δ 8.01 (1H, s), 7.98 (1H, s), 7.46-7.30 (5H, m), 7.25 (2H, d, J 8.5Hz), 6.99 (2H, d, J 8.5Hz), 5.28 (2H, s) and 5.09 (2H, s).

INTERMEDIATE 50

4-Hydroxybenzyl-1,2,4-triazole

Intermediate 49 (1.3g, 5.4mmol) in ethanol (20ml) was hydrogenated at atmospheric pressure over 10% palladium on carbon (100mg) for 6h. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* yielding the title compound (650mg). ^{1}H NMR ($CDCl_3$) δ 8.82 (1H, s),

7.82 (1H, s), 7.62 (1H, s), 6.87 (2H, d, J 8.5Hz), 6.58 (2H, d, J 8.5Hz) and 4.99 (2H, s).

INTERMEDIATE 51

t-Butyl-3-(4-fluorophenyl)-3-[2-[4-(1*H*-1,2,4-triazol-1-ylmethyl)phenoxy]-4-pyrimidinyl]propanoate

The title compound (1.15g, 69%) was prepared from Intermediate 50 (0.63g, 3.6mmol) and Intermediate 11 (1.21g, 3.6mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.1Hz), 8.10 (1H, s), 7.99 (1H, s), 7.33 (2H, d, J 8.5Hz), 7.28-7.19 (4H, m), 6.99 (2H, t, J 8.5Hz), 6.78 (1H, d, J 5.1Hz), 5.49 (2H, s), 4.44 (1H, t, J 6.5Hz), 3.23 (1H, dd, J 16.5, 8.5Hz), 2.79 (1H, dd, J 16.5, 7.0Hz) and 1.32 (9H, s).

INTERMEDIATE 52

4-Benzyloxybenzyl-1,3-benzylimidazole

The title compound (1.1g, 75%) was prepared from Intermediate 43 (1.0g, 4.7mmol) and benzimidazole (1.4g, 11.9mmol) in a similar manner to Intermediate 49. ^{1}H NMR ($CDCl_3$) δ 7.93 (1H, s), 7.82 (1H, m), 7.44-7.22 (8H, m), 7.16 (2H, d, J 8.5Hz), 6.94 (2H, d, J 8.5Hz), 5.31 (2H, s) and 5.04 (2H, s).

INTERMEDIATE 53

4-Hydroxybenzyl-1,3-benzimidazole

The title compound (0.56g, 71%) was prepared from Intermediate 52 (1.1g, 3.5mmol) in a similar manner to Intermediate 50. ^{1}H NMR ($CDCl_3$) δ 8.76 (1H, s), 7.62 (1H, s), 7.34 (1H, m), 6.99 (1H, m), 6.85 (1H, m), 6.73 (2H, d, J 8.5Hz), 6.41 (2H, d, J 8.5Hz) and 4.96 (2H, s).

INTERMEDIATE 54

t-Butyl-3-[2-[4-(1*H*-1,3-benzimidazol-1-ylmethyl)phenoxy]-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate

The title compound (0.95g, 73%) was prepared from Intermediate 53 (0.55g, 2.50mmol) and Intermediate 11 (0.84g, 2.50mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.1Hz), 8.01 (1H, s), 7.98 (1H, d, J 7.8Hz), 7.36-7.12 (9H, m), 6.95 (2H, t, J

8.5Hz), 6.89 (1H, d, J 5.1Hz), 5.42 (2H, s), 4.44 (1H, t, J 7.5Hz), 3.22 (1H, dd, J 16.6, 8.5Hz), 2.79 (1H, dd, J 16.6, 7.0Hz) and 1.32 (9H, s).

INTERMEDIATE 55

1-(4-Benzyloxybenzyl)-2-nitroimidazole

The title compound (1.3g, 100%) was prepared from Intermediate 43 (0.86g, 4.0mmol) and 2-nitroimidazole (0.5g, 4.4mmol) in a similar manner to Intermediate 49. ^{1}H NMR ($CDCl_3$) δ 7.42-7.32 (5H, m), 7.18 (3H, m), 7.01 (3H, m), 5.54 (2H, s) and 5.09 (2H, s).

INTERMEDIATE 56

2-Amino-1-(4-hydroxybenzyl)imidazole

The title compound (0.6g, 78%) was prepared from Intermediate 55 (1.25g, 4.06mmol) in a similar manner to Intermediate 50. ^{1}H NMR (d^6 DMSO) δ 7.70 (1H, s), 6.95 (2H, d, J 8.5Hz), 6.69 (2H, d, J 8.5Hz), 6.40 (2H, d, J 12.0Hz), 4.74 (2H, s) and 4.57 (2H, br s).

INTERMEDIATE 57

t-Butyl-3-[2-[4-(2-amino-1*H*-imidazol-1-ylmethyl)phenoxy]-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate

The title compound (1.1g, 74%) was prepared from Intermediate 56 (0.57g, 3.02mmol) and Intermediate 11 (1.02g, 3.03mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.33 (1H, d, J 5.1Hz), 7.28-7.13 (6H, m), 6.89 (1H, d, J 5.1Hz), 6.71 (1H, s), 6.69 (2H, t, J 8.5Hz), 6.62 (1H, s), 4.98 (2H, s), 4.46 (1H, t, J 8.5Hz), 3.22 (1H, dd, J 16.5, 8.5Hz), 2.78 (1H, dd, J 16.5, 7.8Hz) and 1.33 (9H, s).

INTERMEDIATE 58

2-Chloro-4-(3-trifluoromethoxyphenylmethyl)pyrimidine

The title compound (1.25g, 75%) was prepared from 3-trifluoromethoxybenzylbromide (1.48g, 5.8mmol) and 2,4-dichloropyrimidine (0.85g, 5.8mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, d, J 5.0Hz), 7.38 (1H, t, J 7.0Hz), 7.21-7.10 (3H, m), 7.03 (1H, d, J 5.0Hz) and 4.12 (2H, s).

INTERMEDIATE 59

Methyl-3-(2-chloro-pyrimidin-4-yl)-3-(3-trifluoromethoxyphenyl) propanoate

The title compound (1.44g, 94%) was prepared from Intermediate 60 (1.23g, 4.26mmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, J 5.0Hz), 7.37 (1H, t, J 8.5Hz), 7.28-7.21 (1H, m), 7.20-7.08 (3H, m), 4.59 (1H, dd, J 7.8, 7.0Hz), 3.67 (3H, s), 3.49 (1H, dd, J 16.5, 8.5Hz) and 2.96 (1H, dd, J 16.5, 6.9Hz).

INTERMEDIATE 60

Methyl-3-(2-(4-[(2-pyridinylamino)methyl]phenoxy)-4-pyrimidinyl)-3-(3-trifluoromethoxyphenyl)propanoate

The title compound (1.35g, 64%) was prepared from Intermediate 59 (1.44g, 4.0mmol) and Intermediate 1 (0.80g, 4.0mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d, J 5.0Hz), 8.12 (1H, d, J 6.5Hz), 7.48-7.05 (9H, m), 6.89 (1H, d, J 5.0Hz), 6.61 (1H, t, J 6.5Hz), 6.43 (1H, d, J 8.5Hz), 4.88 (1H, br s), 4.60-4.47 (3H, m), 3.59 (3H,s), 3.37 (1H, dd, J 16.5, 8.5Hz) and 2.86 (1H, dd, J 16.5, 6.5Hz).

INTERMEDIATE 61

2-Chloro-4-(3-cyanophenylmethyl)pyrimidine

The title compound (1.7g, 73%) was prepared from 3-bromomethyl-benzonitrile (2.0g, 10.2mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.54 (1H, d, J 5.2Hz), 7.62-7.42 (4H, m), 7.08 (1H, d, J 5.2Hz) and 4.14 (2H, s).

INTERMEDIATE 62

Methyl-3-(2-chloro-4-pyrimidinyl)-3-(3-cyanophenyl)propanoate

The title compound (1.44g, 66%) was prepared from Intermediate 61 (1.67g, 7.28mmmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.51 (1H, d, J 5.2Hz), 7.53-7.52 (3H, m), 7.47 (1H, t, J 7.0Hz), 7.12 (1H, d, J 5.2Hz), 4.61 (1H, dd, J 7.8, 7.0Hz), 3.66 (3H, s), 3.47 (1H, dd, J 16.5, 7.8Hz) and 2.97 (1H, dd, J 16.5, 6.5Hz).

INTERMEDIATE 63

Methyl-3-(3-cyanophenyl)-3-(2-(4-[(2-pyridinylamino)methyl] phenoxy)-4-pyrimidinyl)propanoate

The title compound (1.53, 49%) was prepared from Intermediate 62 (2.02g, 6.7mmol) and Intermediate 1 (1.30g, 6.7mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.43 (1H, d, J 5.2Hz), 8.11 (1H, d, J 5.0Hz), 7.59-7.50 (3H, m), 7.49-7.35 (4H, m), 7.16 (2H, d, J 8.5Hz), 6.92 (1H, d, J 5.2Hz), 6.59 (1H, dd, J 7.8, 7.0Hz), 6.46 (1H, d, J 8.5Hz), 4.97 (1H, br s), 4.61 (2H, d, J 7.0Hz), 4.51 (1H, t, J 7.8Hz), 3.51 (3H, s), 3.31 (1H, dd, J 16.5, 8.0Hz) and 2.89 (1H, dd, J 16.5, 7.0Hz).

INTERMEDIATE 64

2-Chloro-4-(3-methoxyphenylmethyl)pyrmidine

The title compound (1.95g, 84%) was prepared from 3-methoxybenzyl-bromide (2.00g, 9.5mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, d, J 5.2Hz), 7.26 (1H, t, J 7.0Hz), 7.04 (1H, d, J 5.2Hz), 6.38-6.29 (3H, m), 4.19 (2H, s) and 3.81 (3H, s).

INTERMEDIATE 65

Methyl-3-(2-chloro-4-pyrimidinyl)-3-(3-methoxyphenyl)propanoate

The title compound (2.43g. 95%) was prepared from Intermediate 64 (1.95g, 8.32mmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, d, J 5.2Hz), 7.24 (1H, t, J 7.5Hz), 7.09 (1H, d, J 5.2Hz), 6.88-6.78 (3H, m), 4.54 (1H, dd, J 8.0, 6.5Hz), 3.81 (3H, s), 3.64 (3H, s), 3.49 (1H, dd, J 16.5, 8.5Hz) and 2.91 (1H, dd, J 16.5, 7.0Hz).

INTERMEDIATE 66

Methyl-3-(3-methoxyphenyl)-3-(2-{4-[(2-pyridinylamino)methyl] phenoxy}-4-pyrimidinyl)propanoate

The title compound (2.95g, 80%) was prepared from Intermediate 65 (2.43g, 7.93mmol) and Intermediate 1 (1.59g, 7.93mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.36 (1H, d, J 5.2Hz), 8.12 (1H, dd, J 4.6, 1.1Hz), 7.47-7.39 (3H, m), 7.23-7.12 (3H, m), 6.87 (1H, d, J 5.2Hz), 6.86-6.78 (4H, m), 6.61 (1H, dd, J 6.9, 6.1Hz), 6.42 (1H, d, J 8.5Hz), 4.88 (1H, br s), 4.57 (2H, d, J 7.0Hz), 4.49 (1H, dd, J 7.8, 7.0Hz), 3.79 (3H, s), 3.59 (3H, s), 3.39 (1H, dd, J 16.5, 8.5Hz) and 2.86 (1H, dd, J 16.5, 6.5Hz).

INTERMEDIATE 67

2-Chloro-4-(4-trifluoromethoxyphenylmethyl)pyrimidine

The title compound (1.9g, 84%) was prepared from 4-trifluoromethoxybenzylbromide (2.0g, 7.84mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, d, J 5.2Hz), 7.29 (2H, d, J 8.5Hz), 7.18 (2H, d, J 8.5Hz), 7.02 (1H, d, J 5.2Hz) and 4.11 (2H, s).

INTERMEDIATE 68

Methyl-3-(2-chloro-4-pyrimidinyl)-3-(4-trifluoromethoxyphenyl) propanoate

The title compound (2.23g, 95%) was prepared from Intermediate 67 (1.88g, 6.52mmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, d, J 5.2Hz), 7.34 (2H, d, J 8.5Hz), 7.17 (2H, d, J 8.5Hz), 7.09 (1H, d, J 5.2Hz), 4.59 (1H, dd, J 7.0, 6.0Hz), 3.67 (3H, s), 3.48 (1H, dd, J 16.5, 8.5Hz) and 2.94 (1H, dd, J 16.5, 6.5Hz).

INTERMEDIATE 69

Methyl-3-(2-(4-[(2-pyridinylamino)methyl]phenoxy)-4-pyrimidinyl)-3-(4-trifluoromethoxyphenyl)propanoate

The title compound (2.25g, 69%) was prepared from Intermediate 68 (2.23g, 6.2mmol) and Intermediate 1 (1.2g, 6.2mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d, J 5.2Hz), 8.13 (1H, d, J 5.3Hz), 7.47-7.39 (3H, m), 7.32, 7.24 (2H, m), 7.20-7.09 (4H, m), 6.88 (1H, d, J 5.2Hz), 6.61 (1H, dd, J 7.8, 7.0Hz), 6.43 (1H, d, J 8.5Hz), 4.89 (1H, br s), 4.59-4.48 (3H, m), 3.61 (3H, s), 3.36 (1H, dd, J 16.5, 8.5Hz) and 2.88 (1H, dd, J 16.5, 6.5Hz).

INTERMEDIATE 70

4-(4-Biphenyl-4-ylmethyl)-2-chloropyrimidine.

The title compound (1.2g, 89%) was prepared from 4-phenylbenzylchloride (1.0g, 4.93mmol) in a similar manner to Intermediate 2. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, J 5.2Hz), 7.64-7.54 (4H, m), 7.48-7.40 (2H, m), 7.39-7.29 (3H, m), 7.07 (1H, d, J 5.2Hz) and 4.18 (2H, s).

INTERMEDIATE 71

Methyl-[3-(4-biphenyl)-3-(2-chloro-4-pyrimidinyl)]propanoate

The title compound (1.43g, 97%) was prepared from Intermediate 70 (1.17g, 4.17mmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, d, J 5.2Hz), 7.59-7.54 (4H, m), 7.48-7.39 (2H, m), 7.39-7.31 (3H, m), 7.13 (1H, d, J 5.2Hz), 4.62 (1H, dd, J 7.8, 6.9Hz), 3.68 (3H, s), 3.53 (1H, dd, J 16.5, 8.5Hz) and 2.98 (1H, dd, J 16.5, 6.5Hz).

INTERMEDIATE 72

Methyl-3-(4-biphenyl)-3-(2-[4-({2-pyridylamino}methyl)phenoxy]-4-pyrimidinyl)propanoate

The title compound (1.50g, 67%) was prepared from Intermediate 71 (1.43g, 4.2mmol) and Intermediate 1 (0.84mg, 4.2mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.2Hz), 8.14 (1H, d, J 6.5Hz), 7.59-7.51 (4H, m), 7.48-7.39 (5H, m), 7.39-7.31 (3H, m), 7.20 (2H, d, J 8.5Hz), 6.93 (1H, d, J 5.2Hz), 6.62 (1H, dd, J 6.9, 6.1Hz), 6.42 (1H, d, J 8.5Hz), 4.88 (1H, br s), 4.59 (3H, m), 3.62 (3H, s), 3.45 (1H, dd, J 16.5, 8.5Hz) and 2.92 (1H, dd, J 16.5, 6.5Hz).

INTERMEDIATE 73

2-Chloro-4-[(4-trifluoromethylphenyl)methyl]pyrimidine

The title compound (2.23g, 74%) was prepared from 4-trifluoromethyl-benzylbromide (2.5g, 10.5mmol) in a similar manner to Intermediate 2. ^{1}H NMR (d^6 DMSO) δ 8.69 (1H, d, J 5.2Hz), 7.68 (2H, d, J 8.5Hz), 7.52 (2H, d, J 8.5Hz), 7.49 (1H, d, J 5.2Hz) and 4.23 (2H, s).

INTERMEDIATE 74

Methyl-3-(2-chloro-4-pyrimidinyl)-3-(4-trifluoromethylphenyl) propanoate

The title compound (1.5g, 53%) was preparped from Intermediate 73 (2.23g, 8.2mmol)in a similar manner to Intermediate 3. (d^6 DMSO) δ 8.68 (1H, d, J 5.2Hz), 7.69 (2H, d, J 7.8Hz), 7.61-7.56 (3H, m), 4.75 (1H, d, J 7.8Hz), 3.53 (3H, s), 3.41 (1H, dd, J 16.5, 8.7Hz) and 3.10 (1H, dd, J 17.4, 6.9Hz).

INTERMEDIATE 75

Methyl-3-(2-[4-[(2-pyridinylamino)methyl]phenoxy)-4-pyrimidinyl)-3-(4-trifluoromethylphenyl)propanoate

The title compound (1.60, 70%) was prepared from Intermediate 74 (1.5g, 4.51mmol) and Intermediate 1 (0.90g, 4.51mmol) in a similar manner to Intermediate 13. ^{1}H NMR (d^6 DMSO) δ 8.44 (1H, d, J 6.5Hz), 7.97 (1H, m), 7.64 (2H, d, J 8.7Hz), 7.54 (2H, d, J 8.7Hz), 7.40-7.32 (3H, m), 7.26 (1H, d, J 6.5Hz), 7.11 (2H, d, J 8.7Hz), 7.01 (1H, d, J 5.2Hz), 6.51 (1H, d, J 8.7Hz), 6.46 (1H, dd, J 6.1, 5.2Hz), 4.67 (1H, t, J 7.0Hz), 4.51 (2H, d, J 7.0Hz), 3.51 (3H, s), 3.30 (1H, dd, J 16.5, 7.0Hz) and 2.98 (1H, d, J 16.5, 7.0Hz).

INTERMEDIATE 76

4-Benzyloxybenzonitrile

To a stirred solution of 4-cyanophenol (50g, 0.42mol) and potassium carbonate (150g, 1.1mol) in DMF (800ml) was added benzyl bromide (75ml, 0.63mol). The reaction mixture was stirred for 2h at room temperature before filtering off solid and reducing the filtrate *in vacuo* to give an oil. The solid precipitate was dissolved in water and the pH adjusted to 0.5 using 6.0M hydrochloric acid and extacted into ethyl acetate. The solvent was dried over magnesium sulphate and removed by evaporation *in vacuo* to give an oil. The two oil products were combined and triturated with diethyl ether/hexane to give a white solid, which was washed with hexane and dried to give the title compound (81g, 93%). ^{1}H NMR ($CDCl_3$) δ 7.5 (2H, d, J 8.6Hz), 7.45-7.30 (5H, br m), 7.0 (2H, d, J 8.6Hz) and 5.14 (2H, s). MS (ES) m/e 210 $[M+H]^+$.

INTERMEDIATE 77

4-Benzyloxybenzylamine

To a stirred suspension of lithium alminium hydride (1.75g, 0.46mol) in THF (800ml) at 0° was added 4-benzyloxybenzonitrile (43.0g, 0.23mol) in THF (600ml), dropwise over 4h. The reaction mixture was allowed to warm to room temperature and stirred for 16h and then cooled to 0°. Water (30ml) was added and 2M sodium hydroxide solution (80ml) was then added dropwise with stirring. The resulting precipitate was filtered off washed with diethyl ether (100ml) and toluene (200ml). The filtrate was washed with sodium chloride solution, dried over sodium sulphate and the solvent removed by evaporation *in vacuo*, to give a waxy solid. The two soilds were combined to give the title compound (48.26g, 110%). ^{1}H NMR

($CDCl_3$) δ 7.46-7.25 (5H, br m), 7.23 (2H, d, J 8.75Hz), 6.95 (2H, d, J 8.7Hz), 5.07 (2H, s), 3.81 (2H, s) and 1.50 (2H, br s). MS (ES) m/e 197 [M + NH_4]$^+$.

INTERMEDIATE 78

1-(2-Aminophenyl)-3-(4-benzyloxybenzyl)-2-thiourea

To a stirred solution of 1,1'-thiocarbonyldiimidazole (12.5g, 70mmol) and imidazole (0.95g, 140mmol) in acetonitrile (250ml) at 0° was added Intermediate 77 (11.46g, 53.8mmol) in acetonitrile (150ml) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2.5h and then 1,2-phenylene diamine (10.2g, 90mmol) was added. The reaction mixture was stirred overnight. The cream precipitate was filtered off and dried to give the title compound (14.8g, 88%). ^{1}H NMR (d^6 DMSO) δ 8.87 (1H, s), 7.63 (1H, br s), 7.45-7.28 (5H, b m), 7.25 (2H, d J 8.7Hz), 7.00-6.93 (4H, m), 6.74 (1H, dd, J 8.3, 1.3Hz), 6.56 (1H, td, J 7.5, 1.4Hz), 5.08 (2H, s), 4.62 (2H, d, J 5.4Hz) and 3.32 (2H, s). MS (ES) m/e 364 [M+H]$^+$.

INTERMEDIATE 79

2-(4-(Benzyloxybenzyl)amino)benzimidazole

A stirring solution of Intermediate 78 (3.63g, 0.01mol), mercuric oxide (4.33g, 0.02mol) and sulphur (64mg, 0.03mol) in ethanol (100ml) was heated under reflux for 48h. Upon cooling the reaction mixture was filtered through Celite® and the filtrate solvent removed by evaporation *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate —> 90% ethyl acetate, 10% methanol-silica) giving the title compound as white solid (1.5g, 46%). ^{1}H NMR δ 10.72 (1H, br s), 7.44-7.39 (5H, br m), 7.29 (2H, d, J 8.6Hz), 7.11 (1H, v br s), 7.10 (1H, d, J 8.9Hz), 6.95 (2H, d, J 8.7Hz), 6.99-6.90 (1H, br m), 6.84 (2H, dd, J 5.9, 3.7Hz), 5.07 (2H, s) and 4.42 (2H, d, J 5.9Hz). MS (ES) m/e 330 [M+H]$^+$.

INTERMEDIATE 80

2-(4-(Hydroxybenzyl)amino)benzimidazole

The title compound (7.3g, 100%) was prepared from Intermediate 79 (10.07g, 0.03mol) in a similar manner to Intermediate 50. ^{1}H NMR (d^6 DMSO) δ 10.68 (1H, br s), 9.24 (1H, br s), 7.19-7.10 (5H, m), 6.90-6.81

(4H, m), 6.70 (2H, d, J 8.5Hz) and 4.37 (2H, d, J 5.6Hz). MS (ES) m/e 240 $[M + H]^+$.

INTERMEDIATE 81

Ethyl-3-[2-(4-cyanoanilino)-4-pyrimidinyl]propanoate

Intermediate 12 (5.0g, 23.3mmol) and 4-aminobenzonitrile (2.76g, 23.3mmol) in ethanol (25ml) were heated under refux for 6h. The ethanol was then removed *in vacuo* and the resulting solid triturated with diethyl ether, filtered and dried to give the title compound (6.5g, 94%). ^1H NMR ($CDCl_3$) δ 8.35 (1H, d, J 5.1Hz), 7.77 (2H, d, J 8.8Hz), 7.60 (2H, d, J 8.8Hz), 6.76 (1H, d, J 5.1Hz), 4.13 (2H, q, J 7.1Hz), 3.04 (2H, t, J 7.1Hz), 2.83 (2H, t, J 7.1Hz) and 1.24 (3H, t, J 7.1Hz). MS (ES) m/e 297 $[M + H]^+$.

INTERMEDIATE 82

Ethyl-3-[2-(4-aminomethylanilino)-4-pyrimidinyl]propanoate

The title compound (700mg, 69%) was prepared from Intermediate 81 (1.0g, 3.38mmol) in a similar manner to Intmediate 21. ^1H NMR ($CDCl_3$) δ 8.09 (1H, d, J 5.1Hz), 7.47 (2H, d, J 8.4Hz), 7.12 (2H, d, J 8.4Hz), 6.48 (1H, d, J 5/1Hz), 4.05-3.90 (5H, m), 2.83 (2H, t, J 7.1Hz), 2.66 (2H, t, J 7.1Hz) and 1.07 (3H, t, J 7.1Hz). MS (ES) m/e 301 $[M + H]^+$.

INTERMEDIATE 83

Ethyl-3-[2-(4-([2-pyridinylamino]methyl)anilino)-4-pyrimidinyl] propanoate

The title compound (400mg, 46%) was prepared from Intermediate 82 (700mg, 2.33mmol) in a similar manner to Intermediate 30. ^1H NMR ($CDCl_3$) δ 8.27 (1H,d, J 5.0Hz), 8.11 (1H, dd, J 5.0, 1.0Hz), 7.59 (2H, d, J 8.5Hz), 7.40 (1H, dt, J 7.0, 1.9Hz), 7.32 (2H, d, J 8.4Hz), 7.12 (1H, s), 6.62 (1H, d, J 5.0Hz), 6.59-6.56 (1H, m), 4.90-4.80 (1H, m), 4.46 (2H, d, J 5.7Hz), 4.13 (2H, q, J 7.1Hz), 2.9 (2H, t, J 7.1Hz), 2.81 (2H, t, J 7.1Hz) and 1.23 (3H, t, J 7.1Hz). MS (ES) m/e 378 $[M + H]^+$.

INTERMEDIATE 84

Benzyl-4-bromophenylether

The title compound (6.22g, 82%) was prepared from 4-bromophenol (5.0g, 28.9mmol), benzyl bromide (3.44ml, 28.9mmol) and cesium carbonate

(10.36g, 31.8mmol) in a similar manner to Intermediate 76. ^{1}H NMR ($CDCl_3$) δ 7.50-7.30 (7H, m), 6.86 (2H, d, J 8.8Hz) and 5.05 (2H, s).

INTERMEDIATE 85

Benzyl-4-(6-chloropyridyin-2-yl)phenyl ether

To a solution of Intermediate 84 (2.0g, 7.60mmol) in THF (20ml) at -78° was added n-butyl lithium (1.6M solution in hexanes, 3.34ml, 8.37mmol). The reaction mixture was stirred for 0.5h and zinc chloride (1.14g, 8.37mmol) was added. After a further hour the reaction mixture was warmed to ambient temperature. The reaction was treated with 2,6-dichloropyridine (1.35g, 9.13mmol) and tetrakis(triphenylphosphine) palladium (0) (266mg, 0.23mmol). The reaction was heated under reflux for 18h, then quenched with water, extracted into dichloromethane, dried over sodium sulphate and concentrated *in vacuo*. Recrystallisation from hexane/dichloromethane gave the title compound as a cream powder (2.3g, 100%). ^{1}H NMR ($CDCl_3$) δ 7.96 (2H, d, J 8.9Hz), 7.66 (1H, t, J 7.7Hz), 7.57 (1H, d, J 7.7Hz), 7.57-7.33 (5H, m), 7.19 (1H, d, J 7.7Hz), 7.06 (2H, d, J 8.9Hz) and 5.13 (2H, s).

INTERMEDIATE 86

Benzyl-4-[6-(4-methoxybenzylamino)pyridin-2-yl]phenyl ether

The title compound (0.74g, 33%) was prepared from Intermediate 85 (1.6g, 5.65mmol) and 4-methoxybenzylamine (1.1ml, 8.47mmol) in a similar manner to Intermediate 38. ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, d J 8.7Hz), 7.49-7.37 (6H, m), 7.34 (2H,d, J 8.6Hz), 7.06 (2H, d, J 8.7Hz), 7.02 (1H, d, J 7.6Hz), 6.90 (2H, d, J 8.6Hz), 6.29 (1H d, J 8.2Hz), 5.13 (2H, s), 4.96 (1H, t, J 5.3Hz), 4.52 (2H, d, J 5.6Hz) and 3.81 (3H, s). MS (ES) m/e 397 $[M + H]^+$.

INTERMEDIATE 87

4-[6-(4-Methoxybenzylamino)-pyridin-2-yl] phenol

The title compound (500mg, 87%) was prepared from Intermediate 86 (740mg, 1.87mmol) in a similar manner to Intermediate 50. ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J 8.6Hz), 7.45 (1H, t, J 7.9Hz), 7.26 (2H, d, J 8.6Hz), 6.93 (1H, d, J 7.5Hz), 6.85 (2H, d, J 8.6Hz), 6.73 (2H, d, J 8.6Hz),

6.27 (1H, d, J 8.3Hz), 5.26 (1H, br s), 4.43 (2H, s) and 3.77 (3H, s). MS (ES) m/e 307 $[M + H]^+$.

INTERMEDIATE 88

t-Butyl-3-[2-(4-(2-(4-methoxybenzylamino)-6-pyridinyl)phenoxy)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate

The title compound (300mg, 30%) was prepared from Intermediate 87 (500mg, 1.63mmol) and Intermediate 11 (658mg, 1.96mmol) in DMF in a similar manner to Intermediate 13. ^1H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.14Hz), 8.05 (2H, d, J 8.7Hz), 7.49 (1H, t, J 7.8Hz), 7.33 (2H, d, J 8.7Hz), 7.28-7.22 (4H, m), 7.07 (1H, d, J 7.3Hz), 6.98 (2H, t, J 8.7Hz), 6.90-6.87 (3H, m), 6.34 (1H, d, J 8.1Hz), 4.88 (1H, br s), 4.54 (2H, s), 4.43 (1H, t, J 7.7Hz), 3.80 (3H, s), 3.25 (1H, dd, J 16.1, 8.6Hz), 2.78 (1H, dd, J 16.1, 7.1Hz) and 1.32 (9H, s). MS (ES) m/e 607 $[M + H]^+$.

INTERMEDIATE 89

Benzyl-4-(2-pyrimidyl)phenyl ether

Tetrakis(triphenylphosphine)palladium (0) (185mg, 0.16mmol) was added to a stirred solution of 2-bromopyrimidine (523mg, 3.29mmol) in dioxane (4ml). After 0.5h, 4-benzyloxybenzene boronic acid (8.25mg, 3.62mmol) in dioxane (2ml) and 2M sodium carbonate solution(4.11ml, 8.23mmol) were added. The reaction mixture was heated to reflux for 24h, cooled, quenched with water and extracted into dichloromethane. The organics were dried over sodium sulphate and evaporated. Purification of the residue by flash chomatorgaphy (6:1 hexane, ethyl acetate-silica) gave the title compound (760mg, 88%) ^1H NMR ($CDCl_3$) δ 8.75 (2H, d, J 4.8Hz), 8.41 (2H, d, J 8.9Hz), 7.48-7.32 (5H, m), 7.12 (1H, t, J 4.8Hz), 7.08 (2H, d, J 8.9Hz), and 5.15 (2H, s). MS (ES) m/e 263 $[M + H]^+$.

INTERMEDIATE 90

4-(2-Pyrimidyl)phenol

The title compound (230mg, 46%) was prepared from Intermediate 89 (760mg, 2.90mmol) in a similar manner to Intermediate 50. ^1H NMR (MeOD) δ 8.72 (2H, d, J 4.9Hz), 8.21 (2H, d, J 8.8Hz), 7.21 (1H, t, J 4.9Hz) and 6.86 (2H, d, J 8.9Hz). MS (ES) m/e 173 $[M + H]^+$.

INTERMEDIATE 91

t-Butyl-3-[2-(4-(2-pyrimidinyl)phenoxy)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate

The title compound (400mg, 63%) was prepared from Intermediate 90 (230mg, 1.34mmol) and Intermediate 11 (472mg, 1.40mol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.76 (2H, d, J 4.8Hz), 8.51 (2H, d, J 8.7Hz), 8.36 (1H, d, J 5.0Hz), 7.27 (2H, d, J 8.7Hz), 7.22 (2H, dd, J 8.6, 5.4Hz), 7.14 (1H, t, J 4.8Hz), 6.94 (2H, t, J 8.6Hz), 6.87 (1H, d, J 5.0Hz), 4.11 (1H, dd, J 8.6, 6.9Hz), 3.22 (1H, dd, J 16.1, 8.6Hz), 2.75 (1H,dd, J 16.1, 6.9Hz) and 1.29 (9H, s). MS (ES) m/e 473 $[M + H]^+$.

INTERMEDIATE 92

Benzyl-4-(4,5-dichloro-2-imidazole)phenyl ether

The title compound (510mg, 49%)was prepared from 2-bromo-4,5-dichloroimidazole (710mg, 3.29mmol) in a similar manner to Intermediate 89. ^{1}H NMR ($CDCl_3$) δ 7.70 (2H, d, J 8.9Hz), 7.45-7.31 (5H, m), 7.04 (2H, d, J 8.9Hz) and 5.12 (2H, s). MS (ES) m/e 319 $[M + H]^+$.

INTERMEDIATE 93

4-(2-Imidazole)phenol

The title compound (570mg, 88%) was prepared from Intermediate 92 (1.0g, 3.14mmol) in a similar manner to Intermediate 50. ^{1}H NMR (d^6 DMSO) δ 9.59 (1H, s), 7.72 (2H, d, J 8.5Hz), 7.01 (2H, s), 6.79 (2H, d, J 8.5Hz) and 3.31 (1H, s). MS (ES) m/e 161 $[MH +]^+$.

INTERMEDIATE 94

t-Butyl-3-(2-(4-(2-imidazole)phenoxy)-4-pyrimidinyl)-3-(4-fluorophenyl)propanoate

The title compound (860mg, 91%) was prepared from Intermediate 93 (330mg, 2.06 mmol) and Intermediate 11 (764mg, 2.27mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.28 (1H, d, J 5.0Hz), 7.97 (2H, d, J 8.6Hz), 7.18-7.08 (6H, m), 6.87 (2H, t, J 8.6Hz), 6.80 (1H, d, J 5.0Hz), 4.35 (1H, dd, J 8.5, 7.1Hz), 3.13 (1H, dd J 16.1, 8.5Hz), 2.70 (1H, dd, J 16.1, 7.1Hz) and 1.22 (9H, s). MS (ES) m/e 461 $[M + H]^+$.

INTERMEDIATE 95

t-Butyl-3-[2-((4-(6-(4-methoxybenzyl)amino)-2-pyridinyl)phenoxy)-4-pyrimidinyl]-3-(4-methoxycarbonylphenyl)propanoate

The title compound (700mg, 47%) was prepared from Intermediate 87 (700mg, 2.20mmol) and Intermediate 35 (10.4g, 2.75mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.40 (1H, d, J 5.3Hz), 8.09 (2H, d, J 8.6Hz), 7.98 (2H, d, J 8.7Hz), 7.80-7.73 (1H, m), 7.55 (1H, t, J 7.9Hz), 7.41-7.20 (7H, m), 7.03 (1H, d, J 7.3Hz), 6.90 (2H, d, J 8.7Hz), 6.38 (1H, d, J 7.9Hz), 4.49-4.58 (3H, m), 3.90 (3H, s), 3.30 (3H, s), 3.31 (1H, dd, J 16.5, 8.5Hz), 2.84 (1H, dd, J 16.5, 7.4Hz) and 1.33 (9H, s). MS (ES) m/e 647 $[M + H]^+$.

INTERMEDIATE 96

Benzyl-3-bromophenyl ether

The title compound (15.2g, 100%) was prepared from 3-bromophenol (10.0g, 57.8mmol) iin a similar manner to Intermediate 84. ^{1}H NMR ($CDCl_3$) δ 7.43-7.31 (5H, m), 7.15-7.08 (3H, m), 6.90 (1H, d, J 7.7Hz) and 5.03 (2H, s). MS (ES) m/e 263 $[M + H]^+$.

INTERMEDIATE 97

Benzyl-3-(6-chloro-2-pyridinyl)phenyl ether

The title compound (6.0g, 88%) was prepared from Intermediate 96 (6.0g, 22.8mmol) and 2,6-dichloropyridine (4.05g, 27.4mmol) in a similar manner to Intermediate 85. ^{1}H NMR ($CDCl_3$) δ 7.70-7.50 (4H, m), 7.45-7.25 (7H, m), 7.10-7.05 (1H, m) and 5.05 (2H, s). MS (ES) m/e 298.5 $[M + H]^+$.

INTERMEDIATE 98

Benzyl-3-(5-(4-methoxybenzyl)amino-2-pyridinyl)phenyl ether

The title compound (2.0g, 68%) was prepared from Intermediate 97 (2.2g, 7.39mmol) and 4-methoxybenzylamine (1.51ml, 11.6mmol) in a similar manner to Intermediate 38. ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, d, J 8.7Hz), 7.49-7.37 (6H, m), 7.33 (2H, d, J 8.6Hz), 7.06 (2H, d, J 8.7Hz), 7.02 (1H, d, J 7.6Hz), 6.90 (2H, d, J 8.6Hz), 6.30 (1H, d, J 8.2Hz), 5.13 (2H, s), 4.96 (1H, br t, J 5.3Hz), 4.52 (2H, d, J 8.6Hz) and 3.81 (3H, s). MS (ES) m/e 397 $[M + H]^+$.

INTERMEDIATE 99

3-(5-(4-Methoxybenzyl)amino-2-pyridinyl)phenol

The title compound (280mg, 55%) was prepared from Intermediate 98 (650mg, 1.64mmol) in a similar manner to Intermediate 50. ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, s), 7.43 (2H, t, J 7.9Hz), 7.28-7.21 (3H, m), 6.96 (1H, d, J 7.4Hz), 6.90-6.78 (3H, m), 6.32 (1H, d, J 8.3Hz), 4.44 (2H, s) and 3.78 (3H, s). MS (ES) m/e 307 $[M + H]^+$.

INTERMEDIATE 100

***t*-Butyl-3-[2-(3-(5-(4-methoxybenzyl)amino-2-pyridinyl)phenoxy)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoate**

The title compound (150mg, 27%) was prepared from Intermediate 99 (280mg, 0.92mmol) and Intermediate 11 (309mg, 0.92mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.37 (1H, d, J 5.0Hz), 7.89 (1H, d, J 7.9Hz), 7.84 (1H, s), 7.50-7.45 (3H, m), 7.32-7.17 (3H, m), 7.06 (1H, d, J 7.4Hz), 6.92 (2H, t, J 9.7Hz), 6.35 (1H, d, J 7.9Hz), 4.50 (2H, s), 4.42 (1H, dd, J 7.4, 7.1Hz), 3.79 (3H, s), 3.25 (1H, dd, J 16.1, 7.4Hz), 2.77 (1H, dd, J 16.1, 7.1Hz) and 1.30 (9H, s).

INTERMEDIATE 101

Ethyl-3-(2-(4-[(1*H*-1,3-benzimadzol-2-ylamino)methyl]phenoxy)-4-pyrimidinyl)propanoate

The title compound (0.7g, 39%) was prepared from Intermediate 80 (1.0g, 4.66mmol) and Intermediate 12 (1.11g, 4.66mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.0Hz), 7.38 (2H, d, J 8.5Hz), 7.20-7.05 (5H, m), 6.98-6.93 (2H, m), 4.59 (2H, s), 4.10 (2H, q, J 7.1Hz), 3.06 (2H, t, J 7.2Hz), 2.78 (2H, t, J 7.2Hz) and 1.23 (3H, t, J 7.1Hz).

INTERMEDIATE 102

Ethyl-3-[2-(*N*-allyl-4-cyanoanilino)-4-pyrimidinyl]propanoate

Intermediate 81 (1g, 3.38mmol) was dissolved in DMF (10ml) and sodium hydride (60% dispersion in mineral oil, pre-washed with hexane, 0.14g, 3.55mmol) was added followed by allyl bromide (0.59ml, 6.76mmol). The reaction mixture was heated to 120° under a nitrogen atmosphere for 24h and then quenched with saturated sodium hydrogen carbonate solution.

The organics were extracted into dichloromethane, dried over sodium sulphate, filtered and concentrated *in vacuo*. Purification by flash-chromatography (1:3 ethyl acetate, dichloromethane-silica) gave the title compound as a yellow oil (0.62g, 55%). ^{1}H NMR ($CDCl_3$) δ 8.23 (1H, d, J 5.0Hz), 7.60 (2H, d, J 8.7Hz), 7.47 (2H, d, J 8.8Hz), 6.62 (1H, d, J 5.0Hz), 5.15 (2H, d, J 1.3Hz), 4.69-4.67 (2H, m), 4.10 (2H, q, J 7.1Hz), 2.95 (2H, t, J 7.0Hz), 2.72 (2H, t, J 7.0Hz) and 1.22 (3H, t, J 6.2Hz).

INTERMEDIATE 103

Ethyl-3-{2-[4-aminomethyl)-*N*-propylanilino]-4-pyrimidinyl} propanoate

The title compound (0.63g, 100%) was prepared from Intermediate 102 (0.62g, 1.85mmol) in a similar manner to Intermediate 21. ^{1}H NMR (d^6 DMSO) δ 8.13 (1H, d, J 4.9Hz), 7.47 (2H, d, J 8.2Hz), 7.29 (2H, d, J 8.0Hz), 6.61 (1H, d, J 5.0Hz), 4.06-4.00 (4H, m), 3.89 (2H, t, J 7.3Hz), 2.82 (2H, t, J 6.7Hz), 2.66 (2H, t, J 6.8Hz), 1.54 (2H, m), 1.15 (3H, t, J 7.1Hz) and 0.83 (3H, t, J 7.4Hz). MS (ES) m/e 343 $[M+H]^+$.

INTERMEDIATE 104

Ethyl-3-(2-(*N*-propyl-4-[(2-pyridinylamino)methyl]anilino)-4-pyrimidinyl)propanoate

The title compound (0.6g, 77%) was prepared from Intermediate 103 (0.63g, 1.85mmol) in a similar manner to Intermediate 30. ^{1}H NMR ($CDCl_3$) δ 8.13 (2H, d, J 4.9Hz), 7.42-7.30 (3H, m), 7.26-7.21 (2H, m), 6.44-6.42 (2H, m), 4.52 (2H, d, J 5.7Hz), 4.13 (2H, q, J 7.2Hz), 3.91 (2H, m), 2.92 (2H, t, J 7.1Hz), 2.74 (2H, t, J 7.0Hz), 1.71-1.62 (2H, m), 1.25 (3H, t, J 7.1Hz) and 0.91 (3H, t, J 7.4Hz). MS (ES) m/e 420 $[M+H]^+$.

INTERMEDIATE 105

1-Trityl-1*H*-Imidazole

Imidazole (10.0g, 146.9mmol) was added to sodium hydride (60% dispersion in mineral oil, pre-washed in hexane, 6.5g, 161.6mmol) in DMF (200ml), triphenylmethylchloride (41.0g, 146.9mmol) was then added and the reaction mixture stirred at room temperature for 18h. The mixture was poured onto ice and the solid precipitate formed filtered off and partitioned between water and dichloromethane. The organic phase was washed

with brine and dried over sodium sulphate and concentrated *in vacuo* to give the title compound (37.8g, 83%). ^{1}H NMR ($CDCl_3$) δ 7.42-7.03 (1H, m). MS (ES) m/e 311 $[M + H]^+$.

INTERMEDIATE 106

(1-Trityl-1*H*-imidazol-2-yl)-(4-(benzyloxy)phenyl)methanol

Intermediate 105 (10.0g, 32.2mmol) was dissolved in THF (100ml) and cooled to -78°. n-Butyl lithium (1.6M solution in hexanes, 22.14ml, 34.8mmol) was added followed by 4-benzyloxybenzaldehyde (6.84g, 32.2mmol). The reaction mixture was stirred for 3h and partitioned between water and ethyl acetate. The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane→ethyl acetate-silica) gave the title compound (9.29g, 55%). ^{1}H NMR ($CDCl_3$) δ 7.41-7.06 (22H, m), 6.85-6.74 (3H, m), 6.67 (2H, d, J 8.8Hz), 5.02 (2H, s).

INTERMEDIATE 107

Benzyl-4-{(1*H*-imidazol-2-yl)methyl}phenol

Intermediate 106 (6.53g, 12.51mmol) was dissolved in dichloromethane (50ml) and added to trifluoroacetic acid (50ml) and triethylsilane (14.3ml, 86.5mmol). The reaction mixture was stirred under nitrogen overnight and then concentrated *in vacuo*. The residue was then partitioned between 1M hydrochloric acid and ether. The aqueous layer was basified with 10% sodium hydroxide and then extracted into dichloromethane and concentrated *in vacuo*. Purification by flash chromatography (95% dichloromethane, 5% methanol-silica) gave the title compound (0.92g, 28%). ^{1}H NMR ($CDCl_3$) δ 7.42-7.36 (5H, m), 7.17 (2H, d, J 8.6Hz), 6.95 (4H, d, J 8.6Hz), 5.06 (2H, s), 4.08 (2H, s). MS (ES) m/e 265 $[M + H]^+$.

INTERMEDIATE 108

4-(1*H*-Imidazol-2-ylmethyl)phenol

The title compound (0.27g, 45%) was prepared from Intermediate 107 (0.92g, 3.48mmol) in a similar manner to Intermediate 50. ^{1}H NMR (d^6 DMSO) δ 7.00 (2H, d, J 8.6Hz), 6.87 (2H, s), 6.67 (2H, d, J 8.6Hz), 3.82 (2H, s). MS (ES) m/e 175 $[M + H]^+$.

INTERMEDIATE 109

Ethyl-3-(2-(4-[1*H*-imidazol-2-ylmethyl]phenoxy)-4-pyrimidinyl) propanoate

The title compound (0.25g, 46%) was prepared from Intermediate 108 (0.27g, 1.55mmol) and Intermediate 12 (0.33g, 1.55mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.29 (1H, d, J 5.0Hz), 7.19 (2H, d, J 8.5Hz), 7.06-7.02 (2H, m), 6.90-6.88 (3H, m), 4.07-4.00 (4H, m), 3.00 (2H, t, J 7.1Hz), 2.71 (2H, t, J 7.1Hz), 1.16 (3H, t, J 7.1Hz).

INTERMEDIATE 110

[4-(Benzyloxy)phenyl]-(1*H*-imidazol-2-yl)methanol

Intermediate 106 (5.67g, 10.86mmol) was dissolved in CH_3OH (~50ml) and concentrated hydrochloric acid (10ml) was added. The reaction mixture was stirred overnight then basified with saturated sodium hydrogen carbonate solution. The resulting precipitate was collected and triturated with hot toluene to leave the title compound as a white solid (1.59g, 52%). ^{1}H NMR (d^6 DMSO) δ 7.43-7.26 (7H, m), 6.93 (2H, d, J 8.7Hz), 6.86 (2H, s), 6.01 (1H, d, J 4.13Hz), 5.64 (1H, s), 5.01 (2H, s), MS (ES) m/e 281 $[M + H]^+$.

INTERMEDIATE 111

4-[Hydroxy(1H-imidazol-2-yl)methyl]phenol

The title compound (0.67g, 100%) was prepared from Intermediate 110 (1.0g, 3.57mmol) in a similar manner to Intermediate 50. ^{1}H NMR (d^6 DMSO) δ 7.15 (2H, d, J 8.5Hz), 6.89 (2H, s), 6.67 (2H, d, J 8.5Hz), 5.61 (1H, s).

INTERMEDIATE 112

Ethyl-3-(4-fluorophenyl)-3-(2-(4-hydroxy(1*H*-imidazol-2-yl)methyl phenoxy)-4-pyrimidinyl)propanoate

The title compound (0.75g, 45%) was prepared from Intermediate 111 (0.69g, 3.63mmol) and Intermediate 116 (1.08g, 3.63mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.26 (1H, d, J 5.1Hz), 7.41 (2H, d, J 7.1Hz), 7.26-7.19 (4H, m), 7.09 (2H, d, J 8.55Hz), 6.96 (2H, t, J 8.5Hz), 6.83 (2H, d, J 5.1Hz), 5.88 (1H, s), 4.48 (1H, d, J 2.1Hz), 4.10

(2H, q, J 2.9Hz), 3.32-3.24 (1H, m), 2.85-2.77 (1H, m), 1.12 (3H, t, J 7.1Hz) MS (ES) m/e 463 $[M+H]^+$.

INTERMEDIATE 113

2-Chloro-4-(3-bromobenzyl)pyrimidine

The title compound (4.8g, 70%) was prepared from 3-bromobenzyl bromide (6.0g, 24mmol) in a similar manner to Intermediate 2. ^1H NMR ($CDCl_3$) δ 8.50 (1H, d, J 5.1Hz), 7.41 (2H, m), 7.19 (2H, m), 7.03 (1H, m) and 4.07 (2H, s). MS (ES) m/e 285 $[M + H]^+$.

INTERMEDIATE 114

t-Butyl-3-(2-Chloro-4-pyrimidinyl)-3-(3-bromophenyl)propanoate

The title compound (5.59, 83%) was prepared from Intermediate 113 (4.84g, 17.1mmol) in a similar manner to Intermediate 10. ^1H NMR ($CDCl_3$) δ 8.45 (1H, d, J 5.1Hz), 7.40 (2H, m), 7.21 (2H, m), 7.02 (1H, d, J 5.1Hz), 4.47 (1H, dd, J 9.0, 6.5Hz), 3.34 (1H, dd, J 16.3, 9.0Hz), 2.80 (1H, dd, J 16.3, 6.5Hz), 1.35 (9H, s). MS (ES) m/e 419 $[M + Na]^+$.

INTERMEDIATE 115

t-Butyl-3-(3-bromophenyl)-3-(2-(4-[(2-pyridinylamino)methyl] phenoxy)-4-pyrimidinyl)propanoate

The title compound (6.0g, 76%) was prepared from Intermediate 1 (3.10g, 15.5mmol) and Intermediate 114 (5.59g, 14.1mmol) in a similar manner to Intermediate 13. ^1H NMR ($CDCl_3$) δ 8.37 (1H, d, J 5.1Hz), 8.09 (1H, d, J 5.1Hz), 7.44 (5H, m), 7.17 (6H, m), 6.86 (1H, d, J 5.1Hz), 6.61 (1H, m), 6.43 (1H, d, J 8.5Hz), 4.55 (2H, d, J 5.4Hz), 4.40 (1H, dd, J 8.6, 6.9Hz), 3.23 (1H, dd, J 16.1, 8.6Hz), 2.77 (1H, dd, J 16.1, 8.6Hz), 1.32 (9H, s). MS (ES) m/e 562.9 $[M + H]^+$.

INTERMEDIATE 116

Ethyl-3-(2-chloro-4-pyrimidinyl)-3-(4-fluorophenyl)propanoate

The title compound (13.8g, 94%) was prepared from Intermediate 2 (10.0g, 44.4mmol) and ethyl bromoacetate (7.52g, 45mmol) in a similar manner to Intermediate 3. ^1H NMR ($CDCl_3$) δ 8.45 (1H, d, J 5.1Hz), 7.26 (2H, m), 7.04 (3H, m), 4.55 (1H, dd, J 8.7, 6.5Hz), 4.07 (2H, m), 3.43 (1H,

dd, J 16.6, 8.7Hz), 2.90 (1H, dd, J 16.6, 6.0Hz) and 1.18 (3H, t, J 7.2Hz). MS (ES) m/e 309 $[M+H]^+$.

INTERMEDIATE 117

Methyl-4-benzyloxybenzoate

The title compound (26.6g, 110%) was prepared from methyl 4-hydroxybenzoate (15.2g, 125mmol) utilising sodium hydride as base, in a similar manner to Intermediate 76. ^1H NMR ($CDCl_3$) δ 8.00 (2H, d, J 8.9Hz), 7.82-7.73 (5H, br m), 6.99 (2H, d, J 8.9Hz), 5.12 (2H, s) and 3.89 (3H, s). MS (ES) m/e 243 $[M + H]^+$.

INTERMEDIATE 118

4-Benzyloxybenzoic acid

A solution of Intermediate 117 (26.6g, 109mol) in a mixture of dioxane (200ml), THF (200ml) and water (250ml) was treated with lithium hydroxide mono hydrate (6.3g, 150mmol) and the reaction mixture stirred for 16h at 20°. The solvents were removed *in vacuo* and the residue partitioned between water and ether to give a white solid. This was filtered off as crop 1. The filtrate was extracted with ether dried over magnesium sulphate and evaporated *in vacuo* to give crop 2. The two crops were combined, dissolved in methanol/water and acidified to pH1 with 6M aqueous hydrochloric acid. The white precipitate was filtered off washed well with water and dried under high vacuum to give the title compound as a white solid (20.2g, 88%). ^1H NMR ($CDCl_3$) δ 8.06 (2H, d, J 8.8, 2.2Hz), 7.45-7.36 (5H, m), 7.02 (2H, d, J 8.8, 2.0Hz) and 5.14 (2H, s).

INTERMEDIATE 119

(2-Trimethylsilyl)ethyl 4-benzyloxybenzoate

To a stirred solution of Intermediate 118 (20.2g, 90mmol), DMAP (2.2g, 20mmol), and 2-(trimethylsilyl)ethanol (19ml, 130mmol), in dichloromethane was added 1,2-dicyclohexylcarbolimide (20.1g, 100mmol). The reaction mixture was stirred at room temperature for 16h before being evaporated *in vacuo* to a white solid. The solid was triturated with diethyl ether and the white precipitation removed by filtration. The filtrate was evaporated *in vacuo* to give the title compound as a colourless

oil (31.1g). ^{1}H NMR ($CDCl_3$) δ 7.99 (2H, m), 7.45-7.30 (5H, br m), 6.99 (2H, m), 5.12 (2H, s), 4.39 (2H, m), 1.11 (2H, m) and 0.08 (9H, s).

INTERMEDIATE 120

4-[(2-Trimethylsilyl)ethyloxycarbonyl]phenol

The title compound (21.5g, 96%) was prepared from Intermediate 119 (31.1g, 80mmol) in a similar manner to Intermediate 50. ^{1}H NMR ($CDCl_3$) δ 7.90 (2H, d, J 8.8Hz), 6.86 (2H, d, J 8.8Hz), 4.37 (2H, m), 1.08 (2H, m) and 0.07 (9H, s).

INTERMEDIATE 121

Benzyl-3-(2-chloro-4-pyrimidinyl)-3-(4-fluorophenyl)propanoate

The title compound (12.6g, 78%) was prepared from Intermediate 2 (9.7g, 43.6mmol) and benzyl bromoacetate (7.05ml, 44.5mmol) in a similar manner to Intermediate 3. ^{1}H NMR ($CDCl_3$) δ 8.45 (1H, d, J 5.1Hz), 7.30 (7H, m), 7.00 (3H, m), 5.10 (2H, s), 4.50 (1H, m), 3.50 (1H, m) and 2.95 (1H, m). MS (ES) m/e 371 $[M + H]^+$.

INTERMEDIATE 122

Benzyl-3-(4-fluorophenyl)-3-[2-(4-(2-(trimethylsilyl)ethyloxy carbonyl)phenoxy)-4-pyrimidinyl]propanoate

The title compound (4.3g, 87%) was prepared from Intermediate 120 (2.6g, 10.9mmol) and Intermediate 121 (3.23g, 8.71mmol) in a similar manner to Intermediate 15. ^{1}H NMR ($CDCl_3$) δ 8.37 (1H, d, J 5.1Hz), 8.10 (2H, d, J 8.9Hz), 7.34-7.28 (3H, m), 7.30-7.17 (6H, m), 6.96 (2H, t, J 9.4Hz), 6.88 (1H, d, J 5.1Hz), 5.05 (1H, d, J 12.3Hz), 5.0 (1H, d, J 12.3Hz), 4.50 (1H, dd, J 8.7, 6.1Hz), 4.43 (2H, m), 3.37 (1H, dd, J 16.4, 8.7Hz), 2.89 (1H, dd, J 16.4, 6.6Hz), 1.14 (2H, m) and 0.99 (9H, s). MS (ES) m/e 573 $[M + H]^+$.

INTERMEDIATE 123

3-(4-Fluorophenyl)-3-[2-(4-(2-(trimethylsilyl)ethyloxycarbonyl) phenoxy)-4-pyrimidinyl]propanoic acid

To a stirred solution of Intermediate 122 (4.3g, 7.6mmol) and cyclohexene (40ml) in degassed propan-2-ol under nitrogen was added 10% palladium on carbon (500mg) and the mixture heated under reflux for 72h. The

reaction mixture was filtered through Celite® and the solvent removed *in vacuo*. The residue was purified by chromatography (99% dichloromethane, 1% methanol-silica) to give the title compound (1.91g, 52%). ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d, J 5.0Hz), 8.10 (2H, d, J 8.7Hz), 7.25-7.18 (4H, m), 6.98 (2H, t, J 8.6Hz), 6.88 (1H, d, J 5.0Hz), 4.48 (1H, m), 4.46-4.09 (2H, m), 3.35 (1H, dd, J 17.0, 8.8Hz), 2.84 (1H, dd, J 17.0, 6.1Hz), 1.26-1.12 (2H, m) and 0.97 (9H, s). MS (ES) m/e 483 $[M + H]^+$.

INTERMEDIATE 124

Ethyl-3-[2-(4-cyanophenol)-4-pyrimidinyl]propanoate

The title compound (2.2g, 77%) was prepared from 4-cyanophenol (1.19g, 10.0mmol) and Intermediate 12 (2.15g, 10.0mmol) in a similar manner to Intermediate 13. The crude product was used without purification.

INTERMEDIATE 125

Ethyl-3-[2-{4-(aminomethyl)phenyl}-4-pyrimidinyl]propanoate

The title compound (0.6g, 26%) was prepared from Intermediate 124 (2.2g, 7.7mmol) in a similar manner to Intermediate 21. ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d, J 6.0Hz), 7.36 (2H, d, J 8.0Hz), 7.18 (2H, d, J 8.0Hz), 6.92 (1H, d, J 6.0Hz), 4.12 (2H, q, J 8.0Hz), 3.92 (2H, s), 3.07 (2H, t, J 8.0Hz), 2.83 (2H, t, J 8.0Hz) and 1.23 (3H, t, J 8.0Hz).

INTERMEDIATE 126

Ethyl-3-{2-{4-[(4,5-dihydro-1*H*-imidazol-2-ylamino)methyl]phenoxy}-4-pyrimidinyl}propanoate

The title compound (0.38g, 50%) was prepared from Intermediate 125 (0.6g, 2.0mmol) in a similar manner to Intermediate 48. ^{1}H NMR ($CDCl_3$) δ 8.43 (1H, d, J 7.0Hz), 7.40 (2H, d, J 8.0Hz), 7.14 (2H, d, J 8.0Hz), 6.97 (1H, d, J 7.0Hz), 4.53 (2H, s), 4.09 (2H, t, J 8.0Hz), 3.62 (4H, s), 3.03 (2H, t, J 8.0Hz), 2.75 (2H, t, J 8.0Hz) and 1.21 (3H, t, J 8.0Hz).

INTERMEDIATE 127

Benzyl-4-[6-{4-methoxybenzyl)-*N*-methylamino}pyridin-2-yl]phenyl ether

The title compound (640mg, 49%) was prepared from Intermediate 86 (1.27g, 3.20mmol) and methyl iodide (219μl, 3.52mmol) in a similar

manner to Intermediate 102. ^{1}H NMR ($CDCl_3$) δ 8.01 (2H, d, J 8.Hz), 7.51-7.31 (6H, m), 7.23 (2H, d, J 8.7Hz), 7.03 (2H, d, J 8.8Hz), 7.00 (1H, d, J 6.4Hz), 6.85 (2H, d, J 8.7Hz), 6.43 (1H, d, J 8.3Hz), 5.13 (2H, s), 4.86 (2H, s), 3.80 (3H, s) and 3.10 (3H, s). MS (ES) m/e 411 $[M+H]^+$.

INTERMEDIATE 128

4-[6-{(4-Methoxybenzyl)-*N*-methylamino}-pyridin-2-yl]phenol

The title compound (500mg, 100%) was prepared from Intermediate 127 (640mg, 1.62mmol) in a similar manner to Intermediate 50. ^{1}H NMR ($CDCl_3$) δ 7.94 (2H, d, J 8.7Hz), 7.48 (1H, dd, J 8.3, 7.5Hz), 7.22 (2H, d, J 8.7Hz), 6.99 (1H, d, J 7.5Hz), 6.86 (4H, d, J 8.3Hz), 6.42 (1H, d, J 8.3Hz), 4.85 (2H, s), 3.79 (3H, s) and 3.10 (3H, s). MS (ES) m/e 321 $[M+H]^+$.

INTERMEDIATE 129

t-Butyl-3-[6-(4-(2-({4-methoxybenzyl}-*N*-methylamino)pyridin-2-yl} phenoxy)-4-pyrimidinyl]-3-(4-methoxycarbonylphenyl)propanoate

The title compound (600mg, 56%) was prepared from Intermediate 128 (500mg, 1.62mmol) and Intermediate 35 (670mg, 1.78mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.0Hz), 8.10 (2H, d, J 8.7Hz), 7.96 (2H, d, J 8.3Hz), 7.52 (1H, dd, J 8.4, 7.5Hz), 7.37 (2H, d, J 8.3Hz), 7.23 (4H, d, J 8.7Hz), 7.07 (1H, d, J 8.5Hz), 6.87 (1H, d, J 5.0Hz), 6.85 (2H, d, J 8.7Hz), 6.47 (1H, d, J 8.4Hz), 4.87 (2H, s), 4.52 (1H, dd, J 8.6, 6.9Hz), 3.90 (3H, s), 3.79 (3H, s), 3.31 (1H, dd, J 16.3, 8.6Hz), 3.11 (3H, s), 2.83 (1H, dd, J 16.3, 6.9Hz) and 1.42 (9H, s). MS (ES) m/e 661 $[M+H]^+$.

INTERMEDIATE 130

Ethyl-3-(2-[*N*-benzyl-4-cyanoanilino]-4-pyrimidinyl)propanoate

To an ice cold suspension of Intermediate 81 (1.0g, 3.38mmol) in THF was added potassium bis(trimethylsilyl)amide (0.5Min THF, 7.05ml, 3.55mmol). The solution was then cooled to -78° and benzyl bromide (0.8ml, 6.76mmol) was added. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight, quenched with saturated sodium hydrogen carbonate solution and extracted into dichloromethane, dried over sodium sulphate and evaporated *in vacuo*. Purification by flash chromatography (98% dichloromethane, 2% methanol-silica) gave the title

compound as a yellow oil (400mg, 31%). ^{1}H NMR ($CDCl_3$) δ 8.24 (1H, d, J 5.0Hz), 7.56 (2H, d, J 8.8Hz), 7.42 (2H, d, J 8.8Hz), 7.32-7.16 (5H, m), 6.63 (1H, d, J 5.0Hz), 5.35 (2H, s), 4.05 (2H, q, J 7.1Hz), 2.96 (2H, t, J 7.1Hz), 2.67 (2H, t, J 7.1Hz) and 1.20 (3H, t, J 7.1Hz). MS (ES) m/e 387 $[M+M]^+$.

INTERMEDIATE 131

Ethyl-3-[2-[4-aminomethyl-*N*-benzylanilino]-4-pyrimidinyl]propanoate

The title compound (400mg, 99%) was prepared from Intermediate 130 (400mg, 1.04mmol) in a similar manner to Intermediate 21. ^{1}H NMR ($CDCl_3$) δ 8.02 (1H, d, J 5.2Hz), 7.43 (2H, d, J 8.3Hz), 7.26-7.15 (7H, m), 6.54 (1H, d, J 5.2Hz), 5.19 (2H, s), 4.10-3.95 (4H, m), 2.95 (2H, t, J 7.1Hz), 2.68 (2H, t, J 7.1Hz) and 1.56 (3H, t, J 7.1Hz). MS (ES) m/e 391 $[M+H]^+$.

INTERMEDIATE 132

Ethyl-3-[2-[4-[(2-pyridinylamino)methyl]-*N*-benzylanilino]-4-pyrimidinyl]propanoate

The title compound (250mg, 52%) was prepared from Intermediate 131 (400mg, 1.02mmol) in a similar manner to Intermediate 30. ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, d, J 5.0Hz), 8.09 (1H, dd, J 5.0,1.1Hz), 7.42-7.36 (1H, m), 7.31 (2H, d, J 8.4Hz), 7.27-7.19 (7H, m), 6.60-6.55 (1H, m), 6.49 (1H, d, J 5.0Hz), 6.37 (1H, d, J 8.4Hz), 5.24 (2H, s), 5.06-4.97 (1H, m), 4.47 (2H, d, J 5.7Hz), 4.05 (2H, q, J 7.1Hz), 2.93 (2H, t, J 7.1Hz), 2.68 (2H, t, J 7.1Hz) and 1.20 (3H, t, J 7.1Hz). MS (ES) m/e 468 $[M+H]^+$.

INTERMEDIATE 133

2-[4-(Benzyloxy)phenyl]-*N'*-methylethanimidamide

To a cooled (0°) solution of trimethylaluminium (2.0M solution in toluene, 3.25ml) in toluene (50ml) was added portionwise methylamine hydrochloride (438mg, 6.5mmol). The mixture was stirred at room temperature for 20min, then 4-benzyloxyphenylacetonitrile (1.0g, 4.47mmol) in toluene (2ml) was added, and the mixture heated to reflux for 14h. The mixture was allowed to cool and poured onto a slurry of 10g of silica in 50ml of chloroform. The silica slurry was stirred for 30min then filtered. The silica was washed with chloroform (100ml) then the washings

discarded. The silica plug was then washed with methanol (200ml) and the methanol washings concentrated *in vacuo* to yield the title compound as a gummy solid (1.0g, 94%). ^{1}H NMR (d^6 DMSO) δ 7.43-7.21 (7H, m), 6.91 (2H, d, J 10.1Hz), 5.21 (2H, s), 3.61 (2H, s) and 3.12 (3H, s). MS (ES) m/e 255 $[M + H]^+$.

INTERMEDIATE 134

2-(4-Hydroxyphenol)-*N'*-methylethanimidamide

The title compound (600mg, 87%) was prepared from Intermediate 133 (1.03g, 4.2mmol) in a similar manner to Intermediate 50. ^{1}H NMR (d^6 DMSO) δ 7.22 (2H, d, J 8.8Hz), 6.72 (2H, d, J 8.8Hz), 3.62 (2H, s) and 2.8 (3H, s). MS (ES) m/e 165 $[M + H]^+$.

INTERMEDIATE 135

***t*-Butyl-3-(4-fluorophenyl)-3-(2-{4-[(2-imino-2-methylamino)ethyl] phenoxy}-4-pyrimidinyl)propanoate**

The title compound (350mg, 16%) was prepared from Intermediate 134 (600mg, 4.87mmol) and Intermediate 11 (1.6g, 4.8mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.11 (1H, d, J 6.2Hz), 7.31-6.71 (9H, m), 4.32 (1H, t, J 8.2Hz), 3.82 (2H, s), 3.21 (1H, dd, J 15.2, 7.8Hz), 2.72 (3H, s), 2.62 (1H, dd, J 15.0, 7.8Hz) and 1.21 (9H, s). MS (ES) m/e 465 $[M + H]^+$.

INTERMEDIATE 136

***t*-Butyl-3-{2-[4-(*N,N'*-bis-boc[amino(imino)methyl]amino)methyl) phenoxy]-4-pyrimidinyl}-3-[4-(methoxycarbonyl)phenyl]propanoate**

The title compound (1.1g, 19%) was prepared from *p*-cyanophenol (0.95g, 7.97mmol) and Intermediate 35 (3.0g, 7.97mmol) sequentially by the methods used to prepare Intermediates 13, 21 and 27. ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, d, J 5.4Hz), 7.95 (2H, d, J 8.4Hz), 7.42-7.38 (4H, m), 7.14 (2H, d, J 8.6Hz), 6.89 (1H, d, J 5.4Hz), 4.68 (2H, s), 4.51 (1H, t, J 8.2Hz), 3.89 (3H, s), 3.31 (1H, dd, J 16.4, 8.4Hz), 2.81 (1H, dd, J 16.2, 8.4Hz), 1.52 (9H, s), 1.49 (9H, s) and 1.31 (9H, s). MS (ES) 725 $[M + H]^+$.

INTERMEDIATE 137

***N"*-[4-(Benzyloxy)benzyl-2-pyridinecarboximidamide**

The title compound (800mg, 84%) was prepared from Intermediate 77 (1.0g, 4.9mmol) 2-cyanopyridine (312mg, 3.0mmol) and triethylaluminium in a similar manner to Intermediate 133. ^{1}H NMR (d^{6}DMSO) δ 8.58 (1H, d, J 10.0Hz), 8.18 (1H, d, J 10.0Hz), 7.84 (1H, t, J 10.0Hz), 7.51-7.31 (6H, m), 7.21 (1H, t, J 10.Hz), 7.01-6.92 (3H, m), 5.08 (2H, s) and 4.30 (2H, s). MS (ES) m/e 318 $[M + H]^+$.

INTERMEDIATE 138

***N'*-(4-Hydroxybenzyl)-2-pyridinecarboximidamide**

The title compound (470mg, 82%) was prepared from Intermediate 137 (800mg, 2.51mmol) in a similar manner to Intermediate 50. ^{1}H NMR (d^6 DMSO) δ 8.72 (1H, d, J 8.0Hz), 8.17 (1H, d, J 8.2Hz), 7.82 (1H, t, J 8.2Hz), 7.49 (1H, t, J 8.2Hz), 7.19 (2H, d, J 8.3Hz), 6.68 (2H, d, J 8.3Hz) and 4.22 (2H, s). MS (ES) m/e 228 $[M + H]^+$.

INTERMEDIATE 139

***t*-Butyl-3-(4-fluorophenyl)-3-[2-(4-[[(imino(2-pyridinyl)methyl)amino) methyl]phenoxy)-4-pyrimidinyl]propanoate**

The title compound (200mg, 15%) was prepared from Intermediate 138 (476mg, 2.09mmol) and Intermediate 11 (702mg, 2.09mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.53 (1H, d, J 7.8Hz), 8.32 (1H, d, J 7.8Hz), 7.84 (1H, t, J 7.8Hz), 7.42-6.91 (10H, m), 6.81 (1H, d, J 6.2Hz), 4.72 (2H, s), 4.38 (1H, t, J 8.6Hz), 3.21 (1H, dd, J 16.2, 8.6Hz), 2.72 (1H, dd, J 16.2, 8.6Hz) and 1.28 (9H, s). MS (ES) m/e 528 $[M + H]^+$.

INTERMEDIATE 140

Resin bound 3-(4-Fluorophenyl)-3-[2-(4-(2-[trimethylsilyl]ethyl-oxycarbonyl)phenoxy)-4-pyrimidinyl]propanoic acid

A slurry of Wang resin (Advanced Chem Tech, 1.16g, 0.70mmol/g, 0.81mmol equivalent) in a mixture of dichloromethane (4ml) and DMF (4ml) was treated with Intermediate 123, DMAP (99mg, 0.81mmol) and *N,N'*-diisopropylcarbodiimde (0.20g, 1.63mmol). The resulting mixture was agitated at room temperature for 48h, then filtered and the resin washed thoroughly with dichloromethane, DMF and methanol to give the derivatised resin (Intermediate 140).

INTERMEDIATE 141

Resin bound 3-(4-Fluorophenyl)-3-[2-(4-carboxyphenoxy)-4-pyrimidinyl]propanoic acid

Derivatised resin (Intermediate 140) (2.60g) was suspended in DMF (10ml) and treated with tetrabutylammonium fluoride (1.0M solution in THF, 18ml, 18mmol). The resulting mixture was agitated for 1h at room temperature then filtered and the resin washed thoroughly with dichloromethane, DMF and methanol to give the derivatised resin (Intermediate 141).

INTERMEDIATE 142

Resin bound 3-(4-Bromophenyl)-3-[2-(4-{(2-pyridinylamino} methyl) phenoxy)-4-pyrimidinyl]propanoic acid

A slurry of Wang resin (2.0g, 0.70mmol/g, 1.40mmol equivalent) in a mixture of dichloromethane (10mL) and DMF (10mL) was treated with the compound of Example 45 (2.10g, 4.20mmol), DMAP (171mg, 1.40mmol) and *N,N'*-diisopropylcarbodiimide (0.70mL, 4.20mmol). The resulting mixture was agitated at room temperature for 48h, then filtered and the resin washed thoroughly with dichloromethane, DMF and methanol to give the derivatised resin (Intermediate 142).

INTERMEDIATE 143

2-Chloro-4-[(3-methoxycarbonylphenyl]methyl)pyrimidine

The title compound (2.4g, 86%) was prepared from methyl 3-bromomethylbenzoate (2.5g, 10.9mmol) and 2,4-dichloropyrimidine (1.63g, 10.9mmol) in a similar manner to Intermediate 2. ^{1}H NMR (d^6 DMSO) δ 8.67 (1H, d, J 6.5Hz), 7.90 (1H, br s), 7.84 (1H, t, J 6.9Hz), 7.54 (1H, m), 7.47 (2H, m), 4.20 (2H, s), 3.82 (3H, s).

INTERMEDIATE 144

Methyl-3-(2-chloro-4-pyrimidinyl)-3-(3-methoxycarbonylphenyl) propanoate

The title compound (2.60g, 86%) was prepared from Intermediate 143 (2.38g, 9.07mmol) in a similar manner to Intermediate 3. ^{1}H NMR (d^6 DMSO) δ 8.68 (1H, d, J 6.1Hz), 7.92 (1H, s), 7.81 (1H, d, J 8.5Hz), 7.59

(1H, d, J 6.1Hz), 7.47 (1H, t, J 7.8Hz), 4.72 (1H, t, J 7.9Hz), 3.86 (3H, s), 3.53 (3H, s), 3.39 (1H, dd, J 17.0, 8.5Hz), 3.08 (1H, dd, 17.0, 7.8Hz).

INTERMEDIATE 145

Methyl-3-(3-methoxycarbonylphenyl)-3-(2-[4-((2-pyridinylamino)methyl) phenoxy]-4-pyrimidinyl)propanoate

The title compound (0.98g, 51%) was prepared from Intermediate 144 (1.30g, 3.89mmol) and Intermediate 1 (0.78g, 3.89mmol) in a similar manner to Intermediate 13. ^{1}H NMR (d^6 DMSO) δ 8.46 (1H, d, J 6.5Hz), 7.94 (1H, d, J 5.2Hz), 7.90 (1H, s), 7.81 (1H, d, J 7.8Hz), 7.61 (1H, d, J 7.8Hz), 7.42 (1H, t, J 8.0Hz), 7.40-7.30 (3H, m), 7.27 (1H, d, J 6.5Hz), 7.10 (2H, d, J 8.5HZ), 7.04 (1H, t, J 6.5Hz), 6.51-6.43 (2H, m), 4.64 (1H, t, J 6.9Hz), 4.49 (2H, br s), 3.86 (3H, s), 3.49 (3H, s), 3.28 (1H, dd, J 16.5, 8.5Hz), 2.78 (1H, dd, J 16.5, 7.8Hz).

EXAMPLE 1

3-(2-[4-({[Amino(imino)methyl]amino}methyl)anilino]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid

(i) Intermediate 6 (200mg, 0.55mmol) and *N,N'*-bis-boc-1-guanyl-pyrazole (169mg, 0.55mmol) were stirred in acetonitrile (2ml) at room temperature overnight, then heated under reflux for 2h. The reaction was concentrated *in vacuo* and chromatographed (ethyl acetate-silica) to yield 3-{2-[4-(*N,N'*-bis-boc{[amino(imino)methyl]amino}methyl)anilino]-4-pyrimidinyl}-3-(4-fluorophenyl)propanoic acid (100mg). ^{1}H NMR ($CDCl_3$) δ (v. broad spectrum). 8.52 (1H, br m), 8.05 (2H, br m), 7.50 (2H, br m), 7.12 (2H, br m), 7.04 (1H, br m), 6.80 (2H, br m), 6.30 (1H, br m), 4.50 (2H, br m), 4.39 (1H, br m), 3.18 (1H, br m), 2.70 (1H, br m), 1.49 (9H, s) and 1.43 (9H, s). MS (ES) m/e 609 $[M + H]^+$.

(ii) The 3-{2-[4-(*N,N'*-bis-boc{[amino(imino)methyl]amino}methyl) anilino]-4-pyrimidinyl}-3-(4-fluorophenyl)propanoic acid (100mg, 0.16mmol) in dichloromethane (20ml) with trifluoroacetic acid (4ml) was stirred at room temperature for 2h. The reaction was concentrated *in vacuo* and purified by HPLC (55% water, 45% methanol, 0.1% trifluoroacetic acid-C_{18} reverse phase silica) to yield the title compound (60mg). ^{1}H NMR ($CDCl_3$) δ 8.27

(1H, d, J 5.2Hz), 7.72 (2H, d, J 8.7Hz), 7.38 (2H, m), 7.36 (2H, d, J 8.7Hz), 7.03 (2H, t, J 7.8Hz), 6.71 (1H, d, J 5.2Hz), 4.48 (1H, m), 4.37 (2H, s), 3.39 (1H, dd, J 16.5, 8.7Hz) and 2.91 (1H, dd, J 16.5, 7.8Hz). MS (ES) m/e 409 $[M + H]^+$.

EXAMPLE 2

Methyl-3-(4-fluorophenyl)-3-{2-{4-[(2-pyridinylamino)methyl]phenoxy}-4-pyrimidinyl}propanoate

The title compound was prepared from Intermediate 1 (0.68g, 3.4mmol) and Intermediate 3 (1.0g, 3.4mmol) in a similar manner to Intermediate 13. ^1H NMR ($CDCl_3$) δ 8.35 (1H, d, J 5.1Hz), 8.11 (1H, m), 7.41 (3H, m), 7.22 (2H, m), 7.14 (2H, d, J 8.6Hz), 6.97 (2H, t, J 8.7Hz), 6.85 (1H, d, J 5.0Hz), 6.60 (1H, m), 6.40 (1H, d, J 8.4Hz), 4.88 (1H, br t), 4.55 (2H, d, J 5.8Hz), 4.49 (1H, dd, J 8.5, 6.7Hz), 3.5 (3H, s), 3.34 (1H, dd, J 8.51Hz) and 2.84 (1H, dd, J 16.2, 6.7Hz). MS (ES) m/e 459 $[M + H]^+$.

EXAMPLE 3

3-(4-Fluorophenyl)-3-{2-{4-[(2-pyridinylamino)methyl]phenoxy)-4-pyrimidinyl}propanoic acid

The compound of Example 2 (422mg, 0.92mmol) in methanol:water (4ml 1:1) was treated with 0.101M sodium hydroxide (9.21ml, 0.92mmol) and heated under reflux for 18h. The methanol was removed *in vacuo* and the resulting aqueous residue neutralised with 2M hydrochloric acid. The resulting cloudy solution was extracted into dichloromethane, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (ethyl acetate-silica) yielded the title compound as a white foam. ^1H NMR (d^6 DMSO) δ 8.33 (1H, d, J 5.1Hz), 7.84 (1H, d, J 6.7Hz), 7.54 (1H, t, J 8.4Hz), 7.31 (2H, d, J 8.5Hz), 7.19 (2H, m), 7.10 (2H, d, J 8.6Hz), 6.93 (2H, t, J 8.7Hz), 6.83 (1H, d, J 5.1Hz), 6.61 (1H, t, J 6.1Hz), 6.53 (1H, d, J 8.7Hz), 4.53 (1H, q, J 5.3Hz), 4.44 (2H, s), 3.23 (1H, dd, J 16.5, 9.7Hz) and 2.69 (1H, dd, J 16.5, 5.4Hz). MS (ES) m/e 445 $[M + H]^+$.

EXAMPLE 4

Methyl-3-(3,5-difluorophenyl)-3-{2-{4-[(2-pyridinylamino)-methyl] phenoxy)-4-pyrimidinyl}propanoate

The title compound (410mg, 27%) was prepared from Intermediate 1 (0.64g, 3.2mmol) and Intermediate 8 (1.0g, 3.2mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d J 5.0Hz), 7.15 (2H,d, m), 6.90 (1H, d, J 5.0Hz), 6.81 (2H, m), 6.62 (2H, m), 6.42 (1H, d, J 8.4Hz), 5.61 (1H, br s), 4.59 (2H, d, J 6.3Hz), 4.41 (1H, dd, J 8.5, 6.4Hz), 3.60 (3H, s), 3.28 (1H, dd, J 8.5, 6.4Hz) and 2.81 (1H, dd, J 8.5, 6.4Hz). MS (ES) m/e 477 $[M + H]^+$.

EXAMPLE 5

3-(3,5-Difluorophenyl)-3-(2-(4-[(2-pyridinylamino)-methyl]phenoxy)-4-pyrimidinyl)propanoic acid lithium salt

The compound of Example 4 (40mg, 0.088mmol) in THF (10ml) and water (5ml) was stirred at room temperature and lithium hydroxide monohydrate (37mg, 0.88mmol) added. The solution was stirred at room temperature for 72h, then the solvents were removed *in vacuo*, and the crude white solid partitioned between ethyl acetate (10ml) and water (10ml). The water layer was freeze dried and the title compound was obtained as a white solid. ^{1}H NMR (d^6 DMSO) δ 8.29 (1H, d, J 5.1Hz), 7.81 (1H, d, J 5.1Hz), 7.21 (4H, m), 7.09 (1H, d, J 5.1Hz), 6.80 (4H, m), .6.52 (1H, t, J 10.0Hz), 6.42 (1H, t, J 5.8Hz), 6.39 (1H, d, J 8.6Hz), 4.42 (1H, t, J 7.9Hz), 4.34 (2H, s), 2.98 (1H, dd, J 15.6, 8.4Hz) and 2.77 (1H, dd, J 15.2, 7.5Hz). MS (ES) m/e 463 $[M + H]^+$.

EXAMPLE 6

t-Butyl-3-[5-(ethoxycarbonyl)-3-furyl]-3-(2-(4-[(2-pyridinylamino) methyl]phenoxy)-4-pyrimidinyl)propanoate

The title compound (300mg, 21%).was prepared from Intermediate 1 (1.0g, 2.63mmol) and Intermediate 10 (1.0g, 2.63mmol) in a similar manner to Intermediate 13. ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d, J 6.5Hz), 8.02 (1H, m), 7.49 (1H, m), 7.36 (2H, d, J 8.6Hz), 7.12 (2H, d, J 8.6Hz), 7.05 (1H, d, J 5.5Hz), 6.97 (1H, d, J 6.5Hz), 6.68 (1H, t, J 8.6Hz), 6.50 (1H, d, J 8.6Hz), 6.22 (1H, d, J 5.5Hz), 4.60 (1H, t, J 8.6Hz), 4.52 (2H, s), 4.31 (2H,m), 3.14 (1H, dd, J 8.6, 6.3Hz), 2.91 (1H, dd, J 8.6, 6.3Hz) and 1.32 (12H, m). MS (ES) m/e 544 $[M + H]^+$.

EXAMPLE 7

3-[5-(Ethoxycarbonyl)-3-furyl]-3-(2-(4-[(2-pyridinylamino)methyl] phenoxy)-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The compound of Example 6 (300mg) in dichloromethane (2ml) and trifluoroacetic acid (1ml) was stirred for 12h. The solvent was then removed and the crude product subjected to radial chromatography (94% dichloromethane, 5% methanol, 1% trifluoroacetic acid-4mm silica plate) to yield the title compound (180mg, 67%). ^{1}H NMR (d^6 DMSO) δ 8.49 (1H, d, J 6.0Hz), 7.92 (1H, d, J 8.0Hz), 7.81 (1H, t, J 8.0Hz), 7.42 (2H, d, J 8.0Hz), 7.22 (4H, m), 7.02 (1H, d, J 8.0Hz), 6.81 (1H, t, J 8.0Hz), 6.49 (1H, d, J 5.5Hz), 4.62 (1H, t, J 7.7Hz), 4.58 (2H, s), 4.25 (2H, q, J 6.5Hz), 3.15 (1H, dd, J 8.6, 6.3Hz), 2.91 (1H, dd, J 8.6, 6.3Hz) and 1.25 (3H, t, J 8.6Hz).

EXAMPLE 8

3-(2-(4-[(2-Pyridylamino)methyl]phenoxy)-4-pyrimidinyl)propanoic acid

The title compound (0.44g, 50%) was prepared from Intermediate 13 (0.91g, 2.4mmol) in a similar manner to the compound of Example 3. ^{1}H NMR (d^6 DMSO) δ 8.41 (1H, d, J 5Hz), 7.44 (1H, d, J 6Hz), 7.40-7.30 (3H, m), 7.13 (1H, d, J 5Hz), 7.09 (2H, d, J 8Hz), 7.02 (1H, br t, J 6Hz), 6.52-6.42 (2H, m), 4.47 (2H, br s), 2.90 (2H, t, J 7Hz) and 2.62 (2H, t, J 7Hz). MS (ES) m/e 351 $[M+H]^+$.

EXAMPLE 9

3-(2-(4-[(2-Pyridinylamino)methyl]phenoxy)-4-pyrimidinyl)propenoic acid

The title compound (0.23g, 22%) was prepared from Intermediate 15 (0.48g, 1.27mmol) in a similar manner to the compound of Example 3. ^{1}H NMR (d^6 DMSO) δ 8.62 (1H, d, J 5Hz), 7.95 (1H, d, J 1Hz), 7.47 (1H, d, J 5Hz), 7.37 (2H, d, J 9Hz), 7.40-7.34 (1H, m), 7.29 (1H, d, J 16Hz), 7.13 (2H, d, J 9Hz), 7.04 (1H, t, J 6Hz), 6.88 (1H, d, J 16Hz), 6.51 (1H, d, J 8Hz), 6.48-6.45 (1H, m) and 4.48 (2H, d, J 5Hz). MS (ES) m/e 349 $[M+H]^+$.

EXAMPLE 10

3-(4-Cyanophenyl)-3-(-(4-[(2-pyridinylamino)methyl]phenoxy)-4-pyrimidinyl)propanoic acid tirfluoroacetic acid salt

The title compound (775mg, 80%) was prepared from Intermediate 1 (428mg, 2.14mmol) and Intermediate 17 (660mg, 2.14mmol) by the methods used to prepare Intermediate 13 and the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.43 (1H ,d, J 5.2Hz), 7.94 (1H, s), 7.72 (2H, d, J 7.9Hz), 7.50 (2H, d, J 7.9Hz), 7.41-7.21 (3H, m), 7.22 (H, d, J 5Hz), 7.11-6.92 (3H, m), 6.51-6.32 (2H, m), 4.52 (1H, t, J 5.1Hz), 4.41 (2H, s), 3.18-3.01 (1H, m) and 2.87-2.62 (1H, m). MS (ES) m/e 452 [M+ H]$^+$.

EXAMPLE 11

3-(4-Fluorophenyl)-3-(2-[4-((2-pyridinylamino)carbonyl]phenoxy]-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (75mg, 17%) was prepared from Intermediate 19 (220mg, 0.97mmol) and Intermediate 11 (326mg, 0.97mmol) in a similar manner to the compound of Example 10. ^{1}H NMR (d^6 DMSO) δ 8.49 (1H, d, J 5.4Hz), 8.32 (1H, d, J 5.1Hz), 8.21-8.05 (3H, m,), 7.91-7.80 (1H, m), 7.41-7.06 (8H, m), 4.52 (1H, t, J 7.1Hz), 3.22-3.11 (1H, m), 2.88-2.71 (1H, m). MS (ES) m/e 459 [M + H]$^+$.

EXAMPLE 12

3-[2-(4-[[(4-Amino-2-pyridinyl)amino]methyl)phenoxy)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoic acid trifluoroacetic acid salt

The title compound (100mg, 18%) was prepared from Intermediate 23 (500mg, 0.92mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.42 (1H, d, J 5.2Hz), 7.49-7.28 (6H, m), 7.21-7.02 (5H, m), 6.82 (1H, d, J 5.1Hz), 4.51-4.42 (3H, m), 3.11 (1H, dd, J 15.5, 8.1Hz), 2.72 (1H, dd, J 15.5, 7.9Hz). MS (ES) m/e 460 [M + H]$^+$.

EXAMPLE 13

3-(2-[4-((1*H*-1,3-Benzimidazol-2-yl-amino)methyl]phenoxy]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid trifluoroacetic acid salt

The title compound (200mg, 65%) was prepared from Intermediate 24 (350mg, 0.64mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.42 (1H, d, J 5.0Hz), 7.47 (2H, d, J 8.4Hz), 7.25-7.39 (4H, m), 7.22-7.11 (4H, m), 7.18-7.1 (2H, m), 4.61 (2H, d, J 5.1Hz),

4.51 (1H, t, J 7.9Hz), 3.15 (1H, dd, J 16.6, 8.6Hz), 2.75 (1H, dd, J 16.5, 6.7Hz). MS (ES) m/e 484 $[M + H]^+$.

EXAMPLE 14

3-(2-[4-([[Amino(imino)methyl]amino]methyl)benzyl]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid

Intermediate 26 (620mg, 1.47mmol) was dissolved in dichloromethane (10ml) and *N,N*'bis-boc guanyl triflate added (570mg, 1.47mmol). The mixture was stirred for 12h then trifluoroacetic acid (3ml) was added, and the mixture stirred for a further 2h. The solvents were removed *in vacuo*, and the crude foam subjected to radial chromatography (100%dichloromethane —› 10% methanol, 90% dichloromethane + 1 drop trifluoroacetic acid-4mm silica plate). The title compound was isolated as an off white foam (130mg, 22%). ^{1}H NMR (d^6 DMSO) δ 8.54 (1H, d, J 5.5Hz), 7.99-7.90 (1H, m), 7.39-6.99 (9H, m), 4.48 (1H, t, J 8.6Hz), 4.31 (2H, d, J 7.5Hz), 4.15 (2H, s), 3.32, 3.15 (1H, m), 2.91-2.79 (1H, m). MS (ES) m/e 408 $[M + H]^+$.

EXAMPLE 15

3-(2-[4-([[Amino(imino)methyl]amino]methyl)phenoxy]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid

The title compound (130mg, 70%) isolated as a bis hydrate mono trifluoroacetic acid salt was prepared from Intermediate 27 (300mg, 0.45mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.41 (1H, d, J 5.2Hz), 8.04-7.91 (1H, m), 7.41-7.02 (9H, m), 4.48 (1H, t, J 8.2Hz), 4.37 (2H, d, J 7.6Hz), 3.14 (1H, dd, J 16.5, 8.2Hz), 2.81 (1H, dd, J 16.5, 8.2Hz). MS (ES) m/e 410 $[M + H]^+$.

EXAMPLE 16

3-(4-Fluorophenyl)-3-(2-[4-{(2-pyridinylamino)methyl}anilino]-4-pyrimidinyl)propanoic acid

The title compound (57mg, 34%) was prepared from Intermediate 30 (0.18g, 0.38mmol) in a similar manner to the compound of Example 3. ^{1}H NMR ($CDCl_3$) δ 8.14 (1H, d, J 6.0Hz), 7.85 (1H, d, J 4.0Hz), 7.81 (1H, br s), 7.58-7.42 (3H, m), 7.33-7.13 (4H, m), 6.95 (2H, t, J 9.0Hz), 6.60-6.49

(2H, m), 6.42 (1H, d, J 8.0Hz), 4.53 (1H, dd, J 8.0, 6.0Hz), 3.41 (1H, dd, J 16.0, 10.0Hz) and 2.83 (1H, dd, J 16.0, 6.0Hz). MS (ES) m/e 444 $[M+H]^+$.

EXAMPLE 17

3-Phenyl-3-(2-[4-{(2-pyridinylamino)methyl}phenoxy]-4-pyrimidinyl) propanoic acid trifluoroacetic acid salt

The title compound (370mg, 34%) was prepared from Intermediate 33 (1.2g, 2.4mmol) in a similar manner to the compound of Example 7. ^1H NMR (d^6 DMSO) δ 8.91 (1H, br s), 8.41 (1H, d, J 5.2Hz), 7.91 (1H,d, J 6.8Hz), 7.85 (1H, t, J 8.6Hz), 7.41 (2H, d, J 8.6Hz), 7.35-7.10 (8H, m), 7.05 (1H, d, J 8.6Hz), 6.82 (1H, t, J 6.8Hz), 4.58 (2H, s), 4.49 (1H, t, J 8.6Hz), 3.18 (1H, dd, J 16.4, 7.2Hz) and 2.78 (1H, dd, J 15.8, 8.6Hz). MS (ES) m/e 427 $[M + H]^+$.

EXAMPLE 18

3-[4-(Methoxycarbonyl)phenyl]-3-(2-[4-[(2-pyridinylamino)methyl] phenoxy)-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (260mg, 75%) was prepared from Intermediate 36 (310mg, 0.57mmol) in a similar manner to the compound of Example 7. ^1H NMR (d^6 DMSO) δ 8.39 (1H, d, J 8.6Hz), 7.92 (1H, d, J 5.1Hz), 7.81 (2H, d, J 8.6Hz), 7.41 (2H, d, J 8.6Hz), 7.39-7.31 (3H, m), 7.21 (1H, d, J 5.1Hz), 7.08-6.99 (3H, m), 6.52-6.41 (2H, m), 4.52 (1H, t, J 5.1Hz), 4.45 (2H, d, J 5.1Hz), 3.78 (3H, s), 3.25-3.21 (1H, m) and 2.88-2.72 (1H, m). MS (ES) m/e 485 $[M+H]^+$

EXAMPLE 19

***t*-Butyl-3-(4-benzoicacid)-3-(2-[4-{(2-pyridinylamino)methyl}phenoxy]-4-pyrimidinyl) propanoate**

The title compound was prepared from Intermediate 36 (3.1g, 5.7mmol) in a similar manner to the compound of Example 5. ^1H NMR ($CDCl_3$) δ 8.38 (1H, d, J 5.1Hz), 7.96 (3H, m), 7.52 (1H, m), 7.42 (2H, 2, J 8.4Hz), 7.28 (2H, d, J 7.7Hz), 7.10 (2H, d, J 8.5Hz), 6.93 (1H, d, J 5.1Hz), 6.62 (1H, m), 6.50 (1H, m), 4.55 (2H, br s), 4.47 (1H, m), 3.20 (1H, dd, J 16.3, 8.8Hz), 2.81 (1H, dd, J 16.2, 6.7Hz), and 1.32 (9H, 2). MS (ES) m/e 527 $[M + H]^+$.

EXAMPLE 20

3-(4-[2-Aminoethyl]benzamide)-3-(2-[4-{(2-pyridinylamino)methyl}phenoxy]-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (1.0g, 80%) was prepared from Intermediate 37 (1.1g, 1.6mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.45 (1H, d, J 5.1Hz), 8.20 (1H, br s), 7.98 (1H, m), 7.78 (2H, d, J 8.4Hz), 7.52 (1H, m), 7.40 (4H, m), 7.25 (1H, m), 7.25 (2H, m), 6.68 (1H, m), 6.58 (1H, m), 4.57 (3H, m), 3.55 (2H, m), 3.21 (1H, dd, J 16.3, 7.9Hz), 3.05 (2H, m) and 2.90 (1H, dd, J 16.2, 5.7Hz). MS (ES) m/e 513 [M + H]$^+$.

EXAMPLE 21

3-(4-Benzoic acid)-3-(2-[4-{(2-pyridinylamino)methyl}phenoxy]4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (148mg, 83%) was prepared from the compound of Example 19 (200mg, 0.38mmol) in a similar manner to the compound of Example 7. ^{1}H NMR ($CDCl_3$) δ 8.24 (1H, d, J 5.1Hz), 7.78 (2H, d, J 8.3Hz), 7.75 (2H, m), 7.26 (3H, m), 7.16 (2H, d, J 8.3Hz), 7.05 (2H, d, J 8.5Hz), 6.8 (1H, d, J 5.1Hz), 6.72 (2H, m), 4.48 (2H, s), 4.42 (1H, m), 3.13 (1H, dd, J 16.8, 8.9Hz), 2.66 (1H, dd, J 16.9, 6.0Hz). MS (ES) m/e 471 [M + H]$^+$.

EXAMPLE 22

3-[2-(4-[{(Amino(imino)methyl}amino)methyl]-*N*-methylanilino)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoic acid trifluoroacetic acid salt

The title compound (536mg, 83%) was prepared from Intermediate 40 (825mg, 1.2mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.17 (1H, d, J 5.0Hz), 8.07 (1H, br t, J 5.7Hz), 7.36-7.29 (6H, m), 7.10 (2H, t, J 8.9Hz), 6.64 (1H, d, J 5.0Hz), 4.40-4.30 (3H, m), 3.47 (3H, s), 3.16 (1H, dd, J 16.3, 8.7Hz), 2.75 (1H, dd, J 16.3, 6.6Hz), MS (ES) m/e 423 [M + H]$^+$.

EXAMPLE 23

3-(4-Fluorophenyl)-3-(2-[4-[(3,4,5,6-tetrahydro-2*H*-azepin-7-ylamino)methyl]phenoxy)-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (106mg, 60%) was prepared from Intermediate 42 (200mg, 0.39mmol) in a similar manner to the compound of Example 7.

1H NMR (d^6 DMSO) δ 9.77 (1H, br t), 9.38 (1H, br t), 8.44 (1H, d, J 5.1Hz), 7.41 (4H, m), 7.28 (3H, m), 7.17 (2H, d, J 8.9Hz), 4.55 (1H, t, J 6.8Hz), 4.48 (2H, br d, J 4.3Hz), 3.47 (2H, v br s), 3.24 (1H dd, J 16.5, 7.8Hz), 2.86 (1H, dd, J 16.5, 6.9Hz), 1.72 (4H, m) and 1.62 (2H, m).

EXAMPLE 24

3-(4-Fluorophenyl)-3-(2-[4-(1*H*-imidazol-ylmethyl)phenoxy]-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (500mg, 76%) was prepared from Intermediate 47 (750mg, 1.54mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 9.28 (1H, s), 8.43 (1H, d, J 5.0Hz), 7.82 (1H, t, J 1.7Hz), 7.70 (1H, t, J 1.7Hz), 7.48 (2H, d, J 8.6Hz), 7.34 (2H, dd, J 5.5, 8.8Hz), 7.23 (3H, m), 7.10 (2H, t, J 8.9Hz), 5.45 (2H, s), 4.51 (1H, t, J 7.7Hz), 3.18 (1H, dd, J 16.6, 8.8Hz) and 2.83 (1H, dd, J 16.6, 6.7Hz). MS (ES) m/e 419 $[M+H]^+$.

EXAMPLE 25

3-(2-(4-[(4,5-Dihydro-1*H*-imidazol-2-ylamino)methyl]phenoxy)-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid trifluoroacetic acid salt

The title compound (120mg, 45%) was prepared from Intermediate 48 (268g, 0.61mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.74 (1H, m), 8.43 (1H, d, J 5.0Hz), 7.33 (4H, m), 7.15 (5H, m), 4.51 (1H, t, J 7.67Hz), 4.40 (2H, br d, J 6.1Hz), 3.60 (4H, br m), 3.19 (1H, dd, J 16.6, 8.75Hz), 2.83 (1H, dd, J 16.6, 6.6Hz). MS (ES) m/e 436 $[M + H]^+$.

EXAMPLE 26

3-(4-Fluorophenyl)-3-(2-[4-(1*H*-1,2,4-triazol-1-ylmethyl)phenoxy]-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (0.7g, 71%) was prepared from Intermediate 51 (1.14g, 2.34mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.69 (1H, s), 8.42 (1H, d, J 5.1Hz), 8.00 (1H, s), 7.36-7.31 (4H, m), 7.20 (1H, d, J 5.1Hz), 7.17-7.07 (4H, m), 5.44 (2H, s), 4.51 (1H, t, J 8.6Hz), 3.18 (1H, dd, J 16.5, 8.7Hz) and 2.80 (1H, dd, J 16.5, 6.7Hz). MS (ES) m/e 420 $[M+H]^+$.

EXAMPLE 27

3-{2-[4-(1*H*-1,3-Benzyimidazol-1-ylmethyl)phenoxy]-4-pyrimidinyl}-3-(4-fluorophenyl)propanoic acid trifluoroacetic acid salt

The title compound (250mg, 31%) was prepared from Intermediate 54 (0.91g, 1.74mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 9.40 (1H, s), 8.40 (1H, d, J 5.1Hz), 7.80 (2H, m), 7.45 (4H, m), 7.3 0(2H, m), 7.20 (3H, m), 7.10 (2, t, J 8.9Hz), 5.70 (2H, s), 4.50 (1H, dd, J 8.7, 6.8Hz), 3.10 (1H, dd, J 16.6, 8.7Hz), 2.80 (1H, dd, J 16.5, 6.7Hz). MS (ES) m/e 469 $[M+H]^+$.

EXAMPLE 28

3-{2-[4-(2-Amino-1*H*-imidazol-1-ylmethyl)phenoxy)-4-pyrimidinyl}-3-(4-fluorophenyl)propanoic acid trifluoroacetic acid salt

The title compound (550mg, 65%) was prepared from Intermediate 57 (0.95g, 1.94mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.40 (1H, d, J 5.1Hz), 7.80 (2H, br s), 7.31 (4H, m), 7.20 (3H, m), 7.10 (3H, m), 7.01 (1H, s), 5.10 (2H, s), 4.50 (1H, t, J 7.7Hz), 3.20 (1H, dd, J 16.6, 8.8 Hz) and 2.80 (1H, dd, J 16.6, 6.8Hz). MS (ES) m/e 434 $[M+H]^+$.

EXAMPLE 29

3-{2-[4-[(2-Pyridinylamino)methyl]phenoxy}-4-pyrimidinyl)-3-(3-trifluoromethoxyphenyl)propanoic acid

The title compound (1.0g, 74%) was prepared from Intermediate 60 (1.35g, 2.66mmol) in a similar manner to the compound of Example 3. ^{1}H NMR (d^6 DMSO) δ 9.18 (1H, br s), 8.48 (1H, d, J 5.0Hz), 8.01 (1H, d, J 6.5Hz), 7.92 (1H, d, J 7.8Hz), 7.48-7.38 (3H, m), 7.37-7.31 (2H, m), 7.28 (1H, d, J 5.0Hz), 7.24-7.16 (3H, m), 3.22 (1H, dd, J 16.6, 8.7Hz) and 2.88 (1H, dd, J 16.5, 6.8Hz). MS (ES) m/e 511 $[M+H]^+$.

EXAMPLE 30

3-(3-Cyanophenyl)-3-{2-[4-{(2-pyridinylamino)methyl]phenyl}-4-pyrimidinyl)propanoic acid

The title compound (650mg, 44%) was prepared from Intermediate 63 (1.53g, 3.3mmol) in a similar manner to the compound of Example 3. ^{1}H NMR (d^6 DMSO) δ 8.46 (1H, d, J 5.1Hz), 7.82 (1H, t, J 1.5Hz), 7.71-7.64

(2H, m), 7.49 (1H, t, J 7.8Hz), 7.40-7.34 (3H, m), 7.25 (1H, d, J 5.1Hz), 7.1 (2H, d, J 8.5Hz), 7.0 (1H, t, J 6.0Hz), 6.5 (1H, d, J 8.2Hz), 6.48-6.45 (1H, m), 4.59 (1H, t, J 7.7Hz), 4.49 (2H, d, J 4.8Hz), 3.2 (1H, dd, J 16.6, 8.5Hz) and 2.90 (1H, dd, J 16.6, 7.0Hz). MS (ES) m/e 452 $[M+H]^+$.

EXAMPLE 31

3-(3-Methoxyphenyl)-3-[2-[4-[(2-pyridinylamino)methyl]phenoxy]-4-pyrimidinyl]propanoic acid

The title compound (1.7g, 59%) was prepared from Intermediate 66 (2.95g, 6.28mmol) in a similar manner to the compound of Example 3. ^1H NMR (d^6 DMSO) δ 12.1 0(1H, br s), 8.3 0(1H, d, J 5.1Hz), 7.80 (1H, dd, J 4.6, 1.1Hz), 7.51 (1H, t, J 7.6Hz), 7.27 (2H, d, J 8.5Hz), 7.10-7.03 (4H, m), 6.80-6.70 (4H, m), 6.60 (1H, t, J 6.2Hz), 4.40 (2H,s), 4.30 (1H, dd, J 8.9, 6.5Hz), 3.60 (3H, s), 3.10 (1H, dd, J 16.6, 9.0Hz), 2.70 (1H, dd, J 16.6, 6.5). MS (ES) m/e 457 $[M+H]^+$.

EXAMPLE 32

3-[2-[4-[(2-Pyridinylamino)methyl]phenoxy]-4-pyrimidinyl]-3-(4-trifluoromethoxyphenyl)propanoic acid

The title compound (1.35g, 58%) was prepared from Intermediate 69 (2.37g, 4.54mmol) in a similar manner to the compound of Example 3. ^1H NMR (d^6 DMSO) δ 12.20 (1H, br s), 8.40 (1H, d, J 5.1Hz), 7.91 (1H, d, J 5.3Hz), 7.80 (1H, m), 7.39 (4H, m), 7.22 (3H, m), 7.14 (2H, d, J 8.5Hz), 7.00 (1H, d, J 9.0Hz), 6.80 (1H, t, J 6.5Hz), 4.5 (3H, m), 3.16 (1H, dd, J 16.6, 8.8Hz) and 2.82 (1H, dd, J 16.6, 6.7Hz). MS (ES) m/e 511 $[M+H]^+$.

EXAMPLE 33

3-(4-Biphenyl)-3-[2-[4-[(2-pyridinylamino)methyl]phenoxy]-4-pyrimidinyl]propanoic acid

The title compound (850mg, 61%) was prepared from Intermediate 72 (1.47g, 2.77mmol) in a similar manner to the compound of Example 3. ^1H NMR (d^6 DMSO) δ 8.46 (1H, d, J 5.2Hz), 7.97 (1H, d, J 6.5Hz), 7.69 (1H, t, J 7.8Hz), 7.61-7.54 (4H, m), 7.47-7.31 (7H, m), 7.28 (1H, d, J 5.2Hz), 7.19 (2H, d, J 8.5Hz), 6.88 (1H, d, J 8.5Hz), 6.72 (1H, t, J 6.5Hz), 4.54

(3H, br s), 3.27 (1H,dd, J 16.5, 7.8Hz) and 2.89 (1H, dd, J 16.5, 6.5Hz). MS (ES) m/e 503 $[M+H]^+$.

EXAMPLE 34

3-(2-(4-[(2-Pyridinylamino)methyl]phenoxy)-4-pyrimidinyl)-3-(4-trifluoromethylphenyl)propanoic acid

The title compound (0.81g, 54%) was prepared from Intermediate 75 (1.54g, 3.03mmol) in a similar manner to the compound of Example 5. ^1H NMR (d^6 DMSO) δ 8.54 (1H, d, J 5.1Hz), 8.04 (1H, d, J 3.2Hz), 7.74 (2H, d, J 8.3Hz), 7.64 (2H, d, J 8.2Hz), 7.47-7.43 (3H, m), 7.34 (1H, d, J 5.1Hz), 7.19 (2H, d, J 8.5Hz), 7.14 (1H, t, J 6.1Hz), 6.61 (1H, d, J 8.4Hz), 6.58-6.54 (1H, m), 4.71 (1H, t, J 7.7Hz), 4.59 (2H, d, J 4.9Hz), 3.31 (1H, m) and 3.01 (1H, m). MS (ES) m/e 495 $[M+H]^+$.

EXAMPLE 35

3-[-2(-4-[(2-Pyridinylamino)methyl)anilino)-4-pyrimidinyl]propanoic acid

The title compound (332mg, 89%) was prepared from Intermediate 83 (400mg, 1.06mmol) in a similar manner to the compound of Example 5. ^1H NMR (d^6 DMSO) δ 8.29 (1H, d, J 5.0Hz), 7.92 (1H, d, J 3.9Hz), 7.67 (2H, d, J 8.4Hz), 7.42-7.33 (1H, m), 7.22 (2H, d, J 8.4Hz), 6.70 (1H, d, J 5.0Hz), 6.59-6.45 (2H, m), 4.38 (2H, m), 2.84 (2H, t, J 7.1Hz) and 2.69 (2H, t, J 7.1Hz). MS (ES) m/e 350 $[M + H]^+$.

EXAMPLE 36

3-(2-(4-(2-Amino-6-pyridinyl)phenoxy)-4-pyrimidinyl]-3-(4-fluorophenyl)propanoic acid trifluoroacetic acid salt

Intermediate 88 (300mg, 0.49mmol) was dissolved in trifluoroacetic acid (20ml) and the resulting solution stirred for 4h. The trifluoroacetic acid was then removed *in vacuo*. The residue was purified by radial chromatography (5%—›20% methanol in dichloromethane-4mm silica plate). Freeze drying from methanol/water gave the title compound as a white solid (145mg, 69%) ^1H NMR (d^6 DMSO) δ 8.48 (1H, d, J 5.1Hz), 7.93 (2H, d, J 8.6Hz), 7.19-7.10 (3H, m), 6.77 (1H, br s), 4.54 (1H, dd, J 8.8, 6.7Hz), 3.20 (1H, dd J 16.6, 8.8Hz) and 2.83 (1H, dd, J 16.6, 6.7Hz). MS (ES) m/e 431 $[M + H]^+$.

EXAMPLE 37

3-[2-(4-(2-Pyrimidinyl)phenoxy)-4-pyrimidinyl]-3-(4-fluorophenyl) propanoic acid trifluoroacetic acid salt

The title compound (167mg, 47%) was prepared from Intermediate 91 (400mg, 0.85mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.91 (2H, d, J 4.9Hz), 8.50 (1H, d, J 5.0Hz), 8.45 (2H, d, J 8.8Hz), 7.44 (1H, t, J 4.9Hz), 7.40-7.31 (4H, m), 7.25 (1H, d, J 5.0Hz), 7.11 (2H, t, J 8.8Hz), 4.53 (1H, dd, J 8.8, 6.7Hz), 3.19 (1H, dd, J 16.6, 8.8Hz) and 2.81 (1H, dd, J 16.6, 6.7Hz). MS (ES) m/e 417 $[M + H]^+$.

EXAMPLE 38

3-[2-(4-(2-Imidazole)phenoxy)-4-pyrimidinyl]-3-(4-fluorophenyl) propanoic acid trifluoroacetic acid salt

The title compound (232mg, 33%) was prepared from Intermediate 94 (860mg, 1.87mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.50 (1H, d, J 5.0Hz), 8.06 (2H, d, J 8.7Hz), 7.80 (2H, s), 7.49 (2H, d, J 8.7Hz), 7.35 (2H, dd, J 8.6, 5.6Hz), 7.29 (1H, d, J 5.0Hz), 7.12 (2H, t, J 8.9Hz), 4.54 (1H, dd, J 8.8 and 6.7Hz), 3.18 (1H, dd, J 16.6, 8.8Hz) and 2.83 (1H, dd, J 16.6, 6.7Hz). MS (ES) m/e 405 $[M + H]^+$.

EXAMPLE 39

3-[2-(4-(6-Amino-2-pyridinyl)phenoxy)-4-pyrimidinyl]-3-(4-carboxy phenyl)propanoic acid trifluoroacetic acid salt

The title compound (188mg, 20%) was prepared from Intermediate 95 (700mg, 1.08mmol) sequentially by the methods used to prepare the compounds of Examples 5 and 7. ^{1}H NMR (d^6 DMSO) δ 8.49 (1H, d, J 5.0Hz), 7.94 (2H, d, J 8.5Hz), 7.86 (2H, d, J 8.2Hz), 7.78-7.67 (1H, m), 7.44 (2H, d, J 8.2Hz), 7.34 (2H, d, J 8.5Hz), 7.28 (1H, d, J 5.0Hz), 7.15 (1H, d, J 7.4Hz), 6.77-6.62 (1H, m), 4.60 (1H, dd, J 8.6, 6.7Hz), 3.23 (1H, dd, J 16.7, 8.6Hz) and 2.88 (1H, dd, J 16.7, 6.7Hz). MS (ES) m/e 457 $[M + H]^+$.

EXAMPLE 40

3-[2-(3-(5-Amino-2-pyridinyl)phenoxy)-4-pyrimidinyl]-3-(fluorophenyl)propanoic acid

The title compound (149mg, 60%) isolated as a bistrifluoroacetic acid salt was prepared from Intermediate 100 (150mg, 0.24mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.45 (1H, d, J 5.0Hz), 7.85 (1H, d, J 7.9Hz), 7.78 (1H, br s), 7.51-7.42 (2H, m), 7.34 (2H, dd, J 8.7, 5.5Hz), 7.22 (1H, d, J 5.0Hz), 7.17-7.10 (1H, m), 7.09-7.00 (3H, m), 6.42 (1H, d, J 8.1Hz), 6.02-5.98 (1H, m), 4.51 (1H, dd, J 8.8, 6.5Hz), 3.17 (1H, dd, J 16.4, 8.8Hz) and 2.77 (1H, dd, J 16.4, 6.5Hz) MS (ES) m/e 431 $[M + H]^+$.

EXAMPLE 41

3-(2-(4-[(1*H*-1,3-Benzimidazol-2-ylamino)methyl]phenoxy)-4-pyrimidinyl)propanoic acid

The title compound (30mg, 5%) was prepared from Intermediate 101 (700mg, 1.84mmol) in a similar manner to the compound of Example 5. ^{1}H NMR (d^6 DMSO) δ 8.43 (1H, d, J 5.0Hz), 7.48 (2H, d, J 8.5Hz), 7.39 (2H, dd, J 5.9, 3.2Hz), 7.24-7.19 (4H, m), 7.16 (1H, d, J 5.1Hz), 4.67-4.66 (2H, m), 2.91 (2H, t, J 7.2Hz) and 2.64 (2H, t, J 7.2HZ). MS (ES) m/e 390 $[M+H]^+$.

EXAMPLE 42

3-(2-(*N*-Propyl-4-[(2-pyridinylamino)methyl]anilino)-4-pyrimidinyl)propanoic acid

The title compound (68mg, 12%) was prepared from Intermediate 104 (600mg, 1.43mmol) in a similar manner to the compound of Example 5. ^{1}H NMR (d^6 DMSO) δ 8.10 (1H, d, J 4.9Hz), 7.94 (1H, s), 7.35-7.29 (2H, m), 7.18-7.15 (2H, m), 7.00 (1H, m), 6.56-6.44 (3H, m), 4.45 (2H, s), 3.85 (2H, t, J 7.2Hz), 2.73 (2H, t, J 7.1Hz), 2.49 (2H, s), 1.55 (2H, q, J 7.2Hz) and 0.82 (3H, t, J 7.3Hz). MS (ES) m/e 392 $[M+H]^+$.

EXAMPLE 43

3-(2-[4-(1*H*-Imidazol-2-ylmethyl)phenoxy]-4-pyrimidinyl}propanoic acid

The title compound (65mg, 28%) was prepared from Intermediate 109 (250mg, 0.71mmol) in a similar manner to the compound of Example 5.

^{1}H NMR (DMSO) δ 8.44 (1H, d, J 5.0Hz), 7.54 (2H, s), 7.38 (2H, dd, J 6.6, 2.0Hz), 7.19 (3H, dd, J 6.4, 2.1Hz), 4.32 (2H, s), 2.92 (2H, t, J 7.2Hz), 2.65 (2H, t, J 7.3Hz). m/z 325 MH$^+$.

EXAMPLE 44

3-(4-Fluorophenyl)-3-{2-[4-hydroxy-[1*H*-imidazol-2-yl]methylphenoxy}-4-pyrimidinyl)propanoic acid

The title compound (60mg, 39.5%) was prepared from Intermediate 112 (160mg, 0.35mmol) in a similar manner to the compound of Example 5. ^{1}H NMR (d^6 DMSO) δ 8.46 (1H, d, J 5.1HZ), 7.55 (1H, s), 7.40 (2H, m), 7.25 (3H, d, J 5.0Hz), 7.17 (6H, t, J 7.9Hz), 4.55 (2H, dd, J 8.6, 6.8Hz), 3.24 (1H, dd, J 8.8, 6.6Hz), 2.93-2.84 (1H, m). MS (ES) m/e 435 [M+H]$^+$.

EXAMPLE 45

3-(3-Bromophenyl)-3-{2-[4-[(2-pyridinylamino)methyl]phenoxy}-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (5.0g, 93%) was prepared from Intermediate 115 (6.0g, 11.9mmol) in a similar manner to the compound of Example 7. ^{1}H NMR ($CDCl_3$) δ 9.70 (1H, br s), 8.40 (1H, d, J 5.1Hz), 7.80 (2H, m), 7.50-7.00 (10H, m), 6.80 (1H, m), 4.60 (2H, s), 4.45 (1H, m), 3.15 (1H, dd, J 10.0, 17.0 Hz), 2.65 (1H, dd, J 4.8, 17.0Hz). MS (ES) m/e 507 [M + H]$^+$.

EXAMPLE 46

3-{2-[4-[(4,5-Dihydro-1*H*-imidazol-2-ylamino)methyl]phenoxy}-4-pyrimidinyl)propanoic acid

The title compound (0.16g, 13%) isolated as the octa trifluoroacetate salt was prepared from Intermediate 126 (0.38g, 1.03mmol) in a similar manner to the compoud of Example 3. ^{1}H NMR (d^6 DMSO) δ 12.26 (1H, br s), 8.95 (1H, br s), 8.46 (1H, d, J 4.0Hz), 7.36 (2H, d, J 8.0Hz), 7.19 (2H, d, J 8.0Hz), 7.18 (1H, d, J 4.0Hz), 4.41 (2H, t, J 3.0Hz), 3.62 (4H, s), 2.92 (2H, t, J 7.0Hz) and 2.66 (2H, t, J 7.0Hz). MS (ES) m/e 342 [M+H]$^+$.

EXAMPLE 47

3-[2-{4-[2-(*N*-methylamino)-6-pyridinyl]phenoxy}-4-pyrimidinyl]-3-(4-carboxyphenyl)propanoic acid trifluoroacetic acid salt

The title compound (74mg, 17%) was prepared from Intermediate 129 (600mg, 0.91mmol) sequentially by the methods used to prepare the compounds of Examples 5 and 7. ^{1}H NMR (d^6 DMSO) δ 8.48 (1H, d, J 5.0Hz), 8.02 (2H, d, J 8.6Hz), 7.86 (2H, d, J 8.3Hz), 7.66-7.55 (1H, m), 7.45 (2H, d, J 8.3Hz), 7.28 (2H, d, J 8.6Hz), 7.27 (1H, d, J 5.0Hz), 7.10 (1H, d, J 7.3Hz), 6.58 (1H, br s),4.60 (1H, dd, J 8.7, 6.7Hz), 3.24 (1H, dd, J 16.7, 8.7Hz), 2.90 (3H, s), 2.87 (1H, dd, J 16.7, 6.7Hz). MS (ES) m/e 471 $[M+H]^+$.

EXAMPLE 48

3-(2-[4-[(2-Pyridinylamino)methyl]-*N*-benzylanilino]-4-pyrimidinyl) propanoic acid

The title compound (141mg, 59%) was prepared from Intermediate 132 (250mg, 0.54mmol) in a similar manner to the compound of Example 5. ^{1}H NMR (d^6 DMSO) δ 8.17 (1H, d, J 5.0Hz), 7.93 (1H, d, J 5.2Hz), 7.52 (1H, br t, J 7.8Hz), 7.32-7.15 (9H, m), 6.70-6.62 (2H, m), 6.59 (1H, t, J 6.1Hz), 5.23 (2H, s), 4.46 (2H, s), 2.77 (2H, t, J 7.1Hz) and 2.56 (2H, t, J 7.1Hz). MS (ES) m/e 440 $[M+H]^+$.

EXAMPLE 49

3-(4-Fluorophenyl)-3-(2-[4-[(2-imino-2-methylamino)ethyl]phenoxy]-4-(pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (80mg, 26%) was prepared from Intermediate 135 (350mg, 0.75mmol) in a similar manner to the compound of Example 7. ^{1}H NMR (d^6 DMSO) δ 8.41 (1H, d, J 5.6Hz), 7.48-7.29 (4H, m), 7.21-7.00 (5H, m), 4.48 (1H, t, J 8.6Hz), 3.71 (2H, s), 3.15 (1H, dd, J 16.4, 8.6Hz) and 2.90-2.71 (4H,m). MS (ES) m/e 409 $[M + H]^+$.

EXAMPLE 50

3-[2-[4-[([Amino(imino)methyl]amino)methyl]phenoxy]-4-pyrimidinyl]-3-(4-benzoic acid)propanoic acid trifluoroacetic acid salt

The title compound (50mg, 8%) was prepared from Intermediate 136 (1.1g, 1.5mmol) sequentially by the methods used to prepare the compounds of Examples 5 and 7. ^{1}H NMR (d^6 DMSO) δ 8.42 (1H, d, J 6.2Hz), 798-7.92 (2H, d, J 5.8Hz), 7.63 (2H, d, J 8.4Hz), 7.35 (2H, d, J 8.6Hz), 7.25-7.14 (3H, m), 4.61 (6H, t, J 8.6Hz), 4.35 (2H, d, J 7.2Hz),

3.21 (1H, dd, J 16.4, 8.6Hz) and 2.84 (1H, J 16.4, 8.2Hz). MS (ES) 436 $[M + H]^+$.

EXAMPLE 51

3-(4-Fluorophenyl)-3-(2-(4-[({imino(2-pyridinyl)methyl}amino)methyl] phenoxy)-4-pyrimidinyl)propanoic acid trifluoroacetic acid salt

The title compound (70mg, 40%) was prepared from Intermediate 139 (200mg, 0.37mmol) in a similar manner to the compound of Example 7. ^1H NMR (d^6 DMSO) δ 8.58 (1H, d, J 7.8Hz), 8.41 (1H, d, J 7.8Hz), 8.22 (1H, d, J 8.6Hz), 7.92 (1H, t, J 8.6Hz), 7.42-7.10 (10H, m), 4.72 (2H, br s), 4.42 (1H, t, J 8.6Hz), 3.13 (1H, dd, J 16.2, 8.6Hz) and 2.78 (1H, dd, J 16.4, 8.6Hz). MS (ES) m/e 472 $[M + H]^+$.

EXAMPLE 52

3-(4-Fluorophenyl)-3-[2-(4-{guanidinocarbonyl}phenoxy)-4-pyrimidinyl]propanoic acid

A slurry of derivatised resin (Intermediate 141) (120mg) in DMF (2ml) was treated with *N-tert*butyloxycarbonylguanidine (123mg, 0.84mmol), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (319mg, 0.84mmol) and diisopropylethylamine(108mg, 0.84mmol). The resulting mixture was agitated for 18h at room temperature, then filtered and the resin washed with DMF, dichloromethane and methanol. The resin was treated with a solution of trifluoroacetic acid / dichloromethane (1:1, 3ml) for 1h, then filtered. The filtrate was evaporated *in vacuo* to afford the title compound (20mg) as its trifluoroacetic acid salt.
HPLC-MS (see below) Retention time 2.1min, MH^+ 424 .

EXAMPLE 53

3-(4-(3-Chloro-4-fluorophenyl)phenyl)-3-[2-(4-({2-pyridinylamino} methyl)phenoxy)-4-pyrimidinyl]propanoic acid

A slurry of derivatised resin (Intermediate 142) (120mg, 0.08mmol) in anhydrous/degassed DMF (1mL) was treated with 3-chloro-4-fluorophenylboronic acid (18mg, 0.10mmol), potassium carbonate (28mg, 0.20mmol) and tetrakis(triphenylphosphine)palladium (0) (6mg, 0.005mmol). The resulting mixture was heated to 80° and agitated for 18h. The reaction mixture was cooled to room temperature and then

filtered. The resin was washed with DMF, water, dichloromethane and methanol. The resin was treated with a solution of trifluoroacetic acid / dichloromethane (95:5, 1ml) for 1h, then filtered. The filtrate was evaporated to afford the title compound (1mg).
HPLC-MS Retention time 2.35min MH+ 555

The compounds of Examples 54 to 60 were prepared in a similar manner to the compound of Example 53, using the arylboronic acid shown.

EXAMPLE 54

3-(4-(3-Acetamidophenyl)phenyl)-3-[2-(4-({2-pyridinylamino}methyl) phenoxy)-4-pyrimidinyl]propanoic acid

Using derivatised resin (Intermediate 142) and 3-acetamidobenzene boronic acid yielded the title compound.
HPLC-MS Retention time 2.13min MH+ 560

EXAMPLE 55

3-(4-(2-Formylthienyl)phenyl)-3-[2-(4-({2-pyridinylamino}methyl) phenoxy)-4-pyrimidinyl]propanoic acid

Using derivatised resin (Intermediate 142) and 2-formylthiophene-3-boronic acid yielded the title compound.
HPLC-MS Retention time 2.19min MH+ 537

EXAMPLE 56

3-(4-(3,4-Dichlorophenyl)phenyl)-3-[2-(4-({2-pyridinylamino}methyl) phenoxy)-4-pyrimidinyl]propanoic acid

Using derivatised resin (Intermediate 142) and 3,4-dichlorophenyl-boronic acid yielded the title compound.
HPLC-MS Retention time 2.38min MH+ 571

EXAMPLE 57

3-(4-(4-Isopropylphenyl)phenyl)-3-[2-(4-({2-pyridinylamino}methyl) phenoxy)-4-pyrimidinyl]propanoic acid

Using derivatised resin (Intermediate 142) and 4-isopropylphenylboronic acid yielded the title compound.
HPLC-MS Retention time 2.39min MH+ 545

EXAMPLE 58

3-(4-(2-Formylphenyl)phenyl)-3-[2-(4-((2-pyridinylamino)methyl) phenoxy)-4-pyrimidinyl]propanoic acid

Using derivatised resin (Intermediate 142) and 2-formylbenzeneboronic acid yielded the title compound.

HPLC-MS Retention time 2.21min MH+ 531

EXAMPLE 59

3-(4-(1-Naphthyl)phenyl)-3-[2-(4-((2-pyridinylamino)methyl)phenoxy)-4-pyrimidinyl]propanoic acid

Using derivatised resin (Intermediate 142) and 1-naphthaleneboronic acid yielded the title compound.

HPLC-MS Retention time 2.36min MH+ 553

EXAMPLE 60

3-(4-(4-t-Butylphenyl)phenyl)-3-[2-(4-((2-pyridinylamino)methyl)phenoxy)-4-pyrimidinyl]propanoic acid

Using derivatised resin (Intermediate 142) and 4-*t*-butylbenzeneboronic acid yielded the title compound.

HPLC-MS Retention time 2.49min MH+ 559

EXAMPLE 61

3-(3-Benzenecarboxylic acid)-3-(2-(4-[(2-pyridinylamino)methyl] phenoxy)-4-pyrimidinyl)propanoic salt

The title compund (770mg, 84%) was prepared from intermediate 145 (0.97g, 1.95mmol) in a similar manner to the compound of Example 5. ^{1}H NMR (d^6 DMSO) δ 8.46 (1H, d, J 5.0Hz), 7.99-7.97 (1H,m), 7.89 (1H, t, J 1.7Hz), 7.81 (1H, d, J 7.6Hz), 7.58-7.53 (2H, m), 7.42 -7.38 (3H, m), 7.18 (1H, d, J 5.1Hz), 7.13 (2H, d, J 8.7Hz), 6.75 (1H, d, J 8.6Hz), 6.65-6.62 (1H, m), 4.61-4.57 (3H,m), 3.20 (1H, dd, J 16.3, 8.0Hz), 2.89 (1H, dd, J 16.3, 7.1Hz), MS (ES) m/e 471 $[M+H]^+$.

HPLC-MS

A Luna C18(2) 50 x 2.0mm (3µm) column, running a gradient of 95% [0.1% aqueous formic acid], 5% [0.1% formic acid in acetonitrile] to 10% [0.1% aqueous formic acid], 90% [0.1% formic acid in acetonitrile] over 2min, then maintaining the mobile phase at that ratio for a further 1min. Flow rate 0.8ml/min.

MS was acquired by API electrospray in positive ion mode, at 70V, scanning from 150 to 750amu.

The following assays may be used to determine the ability of compounds according to the invention to inhibit $\alpha_v\beta_3$ and $\alpha_v\beta_5$ function.

$\alpha_v\beta_3$ -Dependent Direct Binding Assay

96 Well NUNC immunoplates were coated overnight with a non-blocking anti-β3 monoclonal antibody at 2 µg/ml in Dulbecco's phosphate buffered saline (PBS) and subsequently blocked with 5% ($^{w}/_{v}$)BSA in PBS (Sigma, fraction V) for 60 min. at room temperature. After washing in Tris-buffered saline (TBS: 20mM Tris/150 mM NaCl, pH 7.5), plates then received 100µl of a lysate prepared from JY cells and were incubated for 3h at room temperature. The lysate was made by lysing JY B-lymphoblastoid cells at 5×10^7 cells were ml in TBS containing 1 mM $MnCl_2$,1% ($^{v}/_{v}$) BSA/0.1% ($^{vb}/_{v}$) Tween 20 and were incubated for a further 2 hours at room temperature. Inhibitors were titrated into the fibronectin prior to addition to plates. After washing, streptavidin-peroxidase (Amersham) at 1:500 in TBS/1% ($^{w}/_{v}$) BSA/0.1% ($^{v}/_{v}$)Tween 20 was added and plates incubated for 1h at room temperature. Finally 100µl TMB substrate was added and Absorbance (630nm) measured after 10-15 miunbutes. IC_{50} values for inhibition of adhesion were calculated on the Activity Base curve fitting programme.

$\alpha_v\beta_3$ -Dependent Cell Adhesion Assay

This was a modification of a published method [Stupack *et al.*, Exp,. Cell. Tes. 203, 443-448 (1992)] and employed the JY cell line. These cells are maintained in RPMI 1640 + 10% FCS + 2mM L-glutamine and, when used for assay, were washed in assat medium (RPMI 1640 + 10% FCS), suspended at 4×10^6/ml in the same medium and pretreated with a

blocking monoclonal antibody to CD18 (6.5E, $F(ab')_2$ fragment) for 10 min at room temperature. 96 Well NUNC immunoplates were coated with 100µl 2.5uk/µl human vitronectin in PBS per well for 2h at 37°C; they were then washed 2x in PBS and blocked with 1% ($^{w}/_{v}$) BSA in PBS for 60min at room temperature and washed 2x more in PBS. 2 x 1^{-5} JY per well were added to wells containing compounds serially titrated across the plate and, finally, phorbol-12-myristate-13-acetate at 10ng/ml was added in a final volume of 200µl. After incubation at 37°C for 30min, non-adherent cells were removed by washing 3 x in assay medium, adherent cells were fixed in methanol and stained with 0.25% ($^{w}/_{v}$) Rose Bengal in PBS for 5 min, unbound dye was removed by 3 further washes in PBS and cell-bound dye was released with 1:1 PBS:ethanol. Absorbance at 570nm was then measured. IC_{50} values for inhibition of adhesion were calculated as described above for the direct binding assay.

$\alpha_v\beta_5$-Dependent Cell Adhesion Assay

This assay was based on a published method [Koivunen *et al*, J. Bio. Chem. 268, 20205-20210 (1993)] and employed the human colon adenocarcinoma cell line HT-29. HT-29 Cells were routinely maintained in DMEM + 10% FCS + 2mM L-glutamine and were removed from flasks using trypsin/EDTA, washed 2x in assay medium and suspended at 4 x 10^6/ml in the same medium. The cells were allowed to 'rest' for 15 min. at room temperature before being added (2 x 10^5/well) to wells containing compounds serially titrated across the plate in a final volume of 200µl. The 96 well NUNC immunoplates had been coated with human vit ronectin as described above for the $\alpha_v\beta_3$ assay. After incubation at 37°C for 60min, adhesion was assessed as described above for the $\alpha_v\beta_3$ assay.

In the above assays the preferred compounds of the invention generally have IC_{50} values of 1µM and below.

Claims

CLAIMS

1. A compound of formula (1):

$$Ar—X^1—Ar^1—Z—R$$

wherein:

(1) Ar is a group $R^{1a}N(R^2)L^1Ar^2$- in which:

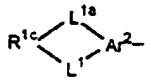
$R^{1a}N(R^2)$ is a nitrogen base;

L^1 is a $-C(R^3)(R^4)$- [where R^3 and R^4, which may be the same or different, is each a hydrogen atom, a straight or branched alkyl group or a hydroxyl group], -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$-, -P(O)-, $-P(O)(OR^a)$- [where R^a is a hydrogen atom or a straight or branched C_{1-6}alkyl group] or $-P(O)(OR^a)O$- group; and

Ar^2 is an optionally substituted six-membered 1,4-arylene or 1,4-heteroarylene ring; or

(2) Ar is a group $R^{1b}Ar^2$ in which R^{1b} is a cyclic or acyclic nitrogen base and Ar^2 is as just defined; or

(3) Ar is a bicyclic ring:



in which R^{1c} is a nitrogen base, L^1 and Ar^2 are as just defined and $-L^{1a}$- is a covalent bond a $-(CH_2)_2$- or $-(CH_2)_3$- group or a group L^1 as just defined; or

(4) Ar is a group $R^{1d}L^1Ar^2$- in which R^{1d} is a nitrogen base and L^1 and Ar^2 as just defined;

X^1 is an -O- or -S- atom or a group selected from -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$-, $-C(R^5)(R^6)$- (where R^5 is a hydrogen atom or an optionally substituted straight or branched alkyl group and R^6 is a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, aromatic, heteroaromatic, or $-(Alk^1)_mR^7$ group [in which Alk^1 is a C_{1-3}alkylene chain, m is zero or the integer 1 and R^7 is a -OH, -SH, $-NO_2$, -CN, $-CO_2H$, $-CO_2R^8$ (where R^8 is an optionally substituted straight or branched C_{1-6}alkyl group), $-SO_3H$,

$-SOR^8$, $-SO_2R^8$, $-OCO_2R^8$, C(O)H, $-C(O)R^8$, $-OC(O)R^8$, $-C(S)R^8$, $-NR^9R^{10}$ (where R^9 and R^{10}, which may be the same or different is each a hydrogen atom or a straight or branched alkyl group), $-C(O)N(R^9)(R^{10})$, $-OC(O)N(R^9)(R^{10})$, $-N(R^9)C(O)R^{10}$, $-CSN(R^9)(R^{10})$, $-N(R^9)C(S)R^{10}$, $-SO_2N(R^9)(R^{10})$, $-N(R^9)SO_2R^{10}$, $-N(R^9)C(O)N(R^{10})(R^{11})$ [where R^{11} is a hydrogen atom or a straight or branched alkyl group], $-N(R^9)C(S)N(R^{10})(R^{11})$, $-N(R^9)SO_2N(R^{10})(R^{11})$, aromatic or heteroaromatic group or $-N(R^5)-$;

Z is a group $-CH(R^{13})CH_2-$ [in which R^{13} is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], $-C(R^{12a})(R^{13})-CH(R^{12b})-$ [in which R^{12a} and R^{12b} together with the carbon atoms to which they are attached form a C_{3-7}cycloalkyl group] or $-C(R^{13})=CH-$;

R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;

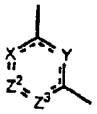
Ar^1 is an optionally substituted 5- or 6-membered nitrogen-containing aromatic or non-aromatic monocycle selected from:

(A)

where one of X and Y is a nitrogen atom and the other is a nitrogen, oxygen or sulphur atom, Z^1 is a carbon, nitrogen, oxygen or sulphur atom and the broken line (- -) represents saturation or unsaturation;

or

(B)

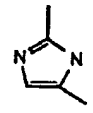


where X, Y and the broken line are as just defined and Z^2 and Z^3 is each a carbon, nitrogen, oxygen or sulphur atom;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 in which R is a $-CO_2H$ group.

3. A compound according to Claim 1 or Claim 2 in which Ar^1 is an optionally substituted aromatic or non-aromatic monocycle selected from :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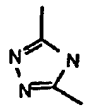
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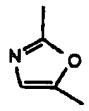
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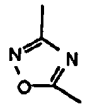
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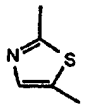
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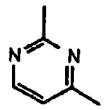
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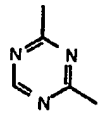
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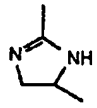
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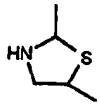
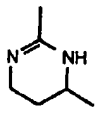

or


4. A compound according to Claim 3 in which Ar^1 is an optionally substituted 2,4-pyrimidinyl group.

5. A compound according to Claim 1 to Claim 4 in which X^1 is a -O-, -S-, -NH- or $-N(CH_3)-$ group.

6. A compound according to Claim 1 to Claim 5 in which L^1 is a group $-C(R^3)(R^4)-$ or -CO-.

7. A compound according to Claim 6 in which L^1 is a group $-CH_2-$.

8. A compound according to Claim 1 to Claim 7 in which Ar is a group $R^{1a}N(R^2)L^1Ar^2$ in which R^2 is a hydrogen atom.

9. A compound according to Claim 8 in which R^{1a} is a group $H_2NC(=NH)$- imidazolinyl, benzimidazlyl or an optionally substituted pyridyl group.

10. A compound according to Claim 1 to Claim 7 in which Ar is a group $R^{1b}Ar^2$ in which R^{1b} is an optionally substituted pyridyl or imidazolyl group.

11. A compound according to Claim 1 to Claim 7 in which Ar is a group $R^{1d}L^1Ar^2$ in which R^{1d} is a group $H_2NC(=NH)$- or an optionally substituted imidazoyl, imidazolinyl, triazolyl or pyridyl group.

12. A compound according to any of the preceding Claims in which Z is a group $-CH(R^{13})CH_2-$ or $-C(R^{13})=CH-$.

13. A compound according to Claim 12 in which R^{13} is an optionally substituted aromatic or heteroaromatic group.

14. A compound according to Claim 13 in which R^{13} is an optionally substituted phenyl or five- or six-membered heteroaromatic group.

15. A compound according to Claim 14 in which R^{13} is an optionally substituted phenyl group.

16. A compound which is:
3-(4-[2-Aminoethyl]benzamide)-3-(2-[4-{(2-pyridinylamino)methyl} phenoxy]-4-pyrimidinyl)propanoic acid;
3-(2-{4-[(4,5-Dihydro-1*H*-imidazol-2-ylamino)methyl]phenoxy}-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid
3-{2-[4-({[Amino(imino)methyl]amino}methyl)phenoxy]-4-pyrimidinyl}-3-(4-benzoic acid)propanoic acid;
3-[2-(4-[({Amino(imino)methyl}amino)methyl]-*N*-methylaniliino)-4-pyrimidinyl]-3-(4-fluorophenol)propanoic acid;

3-(3-Methoxyphenyl)-3-(2-{4-{(2-pyridinylamino)methyl]phenoxy}-4-pyrimidinyl)propanoic acid;

3-[2-(4-{6-Amino-2-pyridinyl}phenoxy)-4-pyrimidinyl]-3-(4-carboxy phenyl)propanoic acid;

3-[2-(4-{2-(*N*-methylamino)-6-pyridinyl}phenoxy)-4-pyrimidinyl]-3-(4-carboxyphenyl)propanoic acid;

3-(2-[4-{(1*H*-1,3-Benzimidazol-2-yl-amino)methyl}phenoxy]-4-pyrimidinyl)-3-(4-fluorophenyl)propanoic acid;

3-(3-Benzenecarboxylic acid)-3-(2-{4-[(2-pyridinylamino)methyl] phenoxy)-4-pyrimidinyl)propanoic acid;

and the salts, solvates, hydrates and N-oxides thereof.

17. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03893

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/505 C07D403/12 C07D239/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 227 490 A (HARTMAN GEORGE D ET AL) 13 July 1993 (1993-07-13) claim 1	1
Y	US 5 773 646 A (CLARE MICHAEL ET AL) 30 June 1998 (1998-06-30) claim 1	1
Y	WO 97 36859 A (RICO JOSEPH G ;SEARLE & CO (US); YU STELLA S (US); CHEN BARBARA B) 9 October 1997 (1997-10-09) claim 1	1

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 2000	3 May 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GETTINS M.P.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/GB 99/03893

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7 (all part),8,9,11-15 (all part),16,17 (part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2

It must be made credible that essentially all of the claimed matter solves the given problem. With the present scope of the claims this is not the case. The expressions in the claims "optionally substituted", "nitrogen base", "aliphatic", "cycloaliphatic", "heteroaliphatic", "aromatic", "heteroaromatic"alkyl" and derivatives thereof as well as "derivative or bioisostere thereof" are non-limitative and are therefore not regarded as obvious modifications or equivalents of the examples which have been given in the description. Accordingly, the said expressions should be restricted in this respect to the particular meanings specified in the description e.g. pp8-20 (Article 6 PCT). It should be borne in mind that only those compounds which are suitable for solving the problem underlying the present application can be claimed. In the light of the huge scope of the claims and the limited scope of the inventions the search has been limited to the compounds in which Ar1 is a 2,4-pyrimidinyl group and R is a COOH group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 99/03893

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-7 (all part),8,9,11-15 (all part),16,17 (part)

   Ar is group (1)

2. Claims: 1-7 (all part),10,11-15 (all part),17 (part)

   Ar is group (2)

3. Claims: 1-7 (all part),11-15 (all part),17 (part)

   Ar is group (3)

4. Claims: 1-7 (all part),11-15 (all part),17 (part)

   Ar is group (4)

INTERNATIONAL SEARCH REPORT

ormation on patent family members

International Application No
PC., GB 99/03893

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5227490 A	13-07-1993	AU 3665793 A	13-09-1993
		WO 9316697 A	02-09-1993
US 5773646 A	30-06-1998	AU 2337097 A	22-10-1997
		CA 2250464 A	09-10-1997
		EP 0889877 A	13-01-1999
		WO 9736862 A	09-10-1997
WO 9736859 A	09-10-1997	AU 2536097 A	22-10-1997
		CA 2250698 A	09-10-1997
		EP 0891325 A	20-01-1999
		US 5952381 A	14-09-1999